Total Synthesis of Daphenylline

2024.2.10. Literature Seminar
B4 Sota Mochizuki

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Introduction of Prof. Y. Yang and R. Sarpong

Prof. Yu-Rong Yang

2000: B.S. @ Lanzhou University
2005: Ph. D. @ Lanzhou University (Prof. W. D. Li)
2005~2007: Postdoc @ Harvard University (Prof. Y. Kishi)
2008~: Professor @ Kunming Institute of Botany, Chinese Academy of Sciences

Research topic:
- Total synthesis of natural products
- Development of new methods and strategies, including applications of asymmetric catalysis

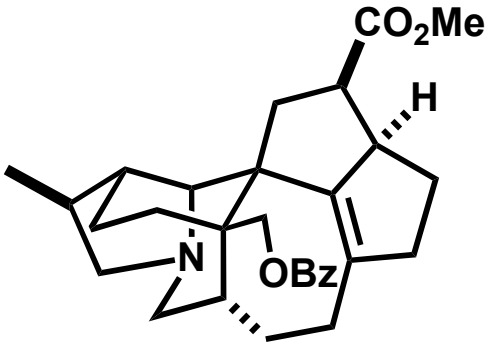
Prof. Richmond Sarpong

1995: B.S. @ Macalester College (Prof. R. C. Hoye)
2001: Ph. D. @ Princeton University (Prof. M. F. Semmelhack)
2000~2004: Postdoc @ California Institute of Technology (Prof. B. M. Stolzs)
2004~2010: Assistant professor @ University of California, Berkeley
2010~2014: Associate professor @ University of California, Berkeley
2014~: Professor @University of California, Berkeley

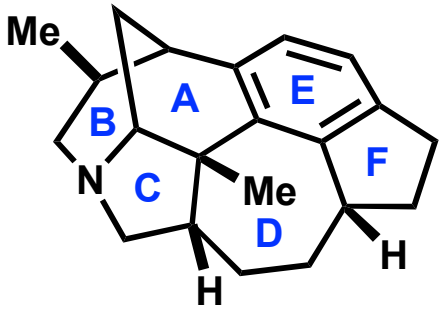
Research topic:
- Total synthesis of natural products
- Development of synthetic methods (C-C bond cleavage)

1) http://groups.english.kib.cas.cn/Phytochem/yyr/People/202210/t20221013_717917.html
2) https://sarponggroup.com/richmond-sarpong/

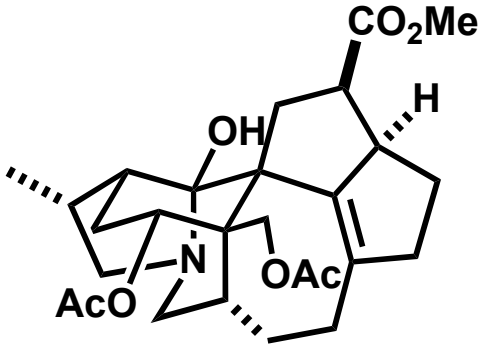
Daphniphyllum Alkaloids



daphangustifoline B



daphenylline



yuzurimine C

Isolation [1]:
the fruits of *Daphniphyllum longeracemosum* (daphenylline, reported in 2009)

Biological activity [2]:
- **cytotoxity against human tumor cell lines (HL-60, P-388, BEL-7402) (daphangustifoline B)**
- **pesticide activity against brine shrimp (yuzurimine C)**

Structural features (of daphenylline):
- **2-azabicyclo[3,3,1]nonane core**
- **fused benzenoid core**
- **6 stereogenic centers**
- **1 all-carbon quaternary center**

Total synthesis (of daphenylline) [3]:
Li (2013, 2018), Fukuyama (2016)
Zhai (2018), Qiu (2019, 2021), Lu (2022)
Yang (2024), Sarpong (2024)

1) Zhang, Q.; Di, Y.-T.; Li, C.-S.; Fang, X.; Tan, C.-J.; Zhang, Z.; Zhang, Y.; He, H.-P.; Li, S.-L.; Hao, X. *J. Org. Lett.* **2009**, *11*, 2357−2359.

2) Wu, H.; Zhang, X.; Ding, L.; Chen, S.; Yang, J.; Xu, X. *Planta. Med.* **2013**, *79*, 1589-1598.

3) (a) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679−684. (b) Chen, Y.; Zhang, W.; Ren, L.; Li, J.; Li, A. *Angew. Chem., Int. Ed.* **2018**, *57*, 952−956. (c) Yamada, R.; Adachi, Y.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 6067−6070. (d) Chen, X.; Zhang, H.-J.; Yang, X.; Lv, H.; Shao, X.; Tao, C.; Wang, H.; Cheng, B.; Li, Y.; Guo, J.; Zhang, J.; Zhai, H. *Angew. Chem., Int. Ed.* **2018**, *57*, 947−951. (e) Xu, B.; Wang, B.; Xun, W.; Qiu, F. G. *Angew. Chem., Int. Ed.* **2019**, *58* (17), 5754−5757. (f) Wang, B.; Xu, B.; Xun, W.; Guo, Y.; Zhang, J.; Qiu, F. G. *Angew. Chem., Int. Ed.* **2021**, *60*, 9439−9443. (g) Cao, M.-Y.; Ma, B.-J.; Gu, Q.-X.; Fu, B.; Lu, H.-H. *J. Am. Chem. Soc.* **2022**, *144*, 5750−5755. (h) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268. (g) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

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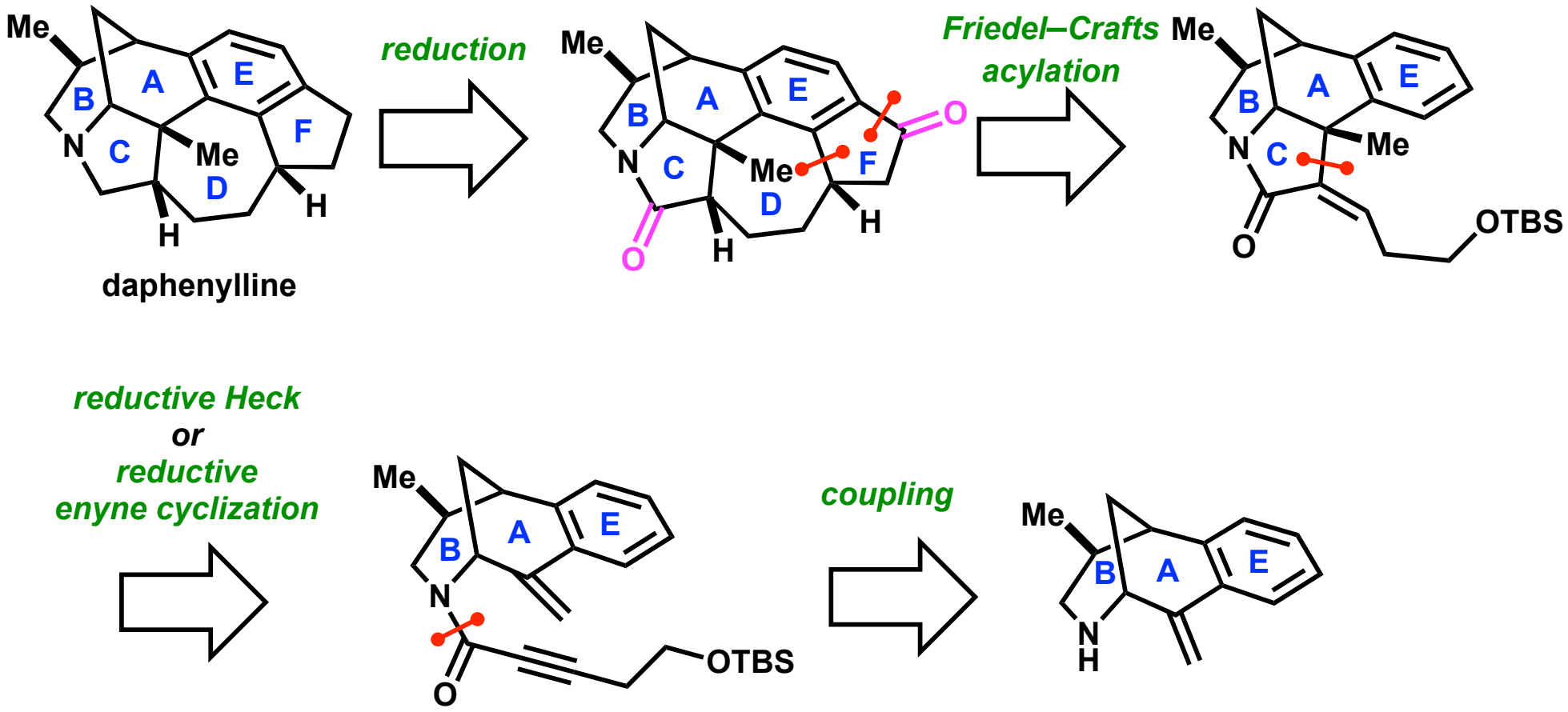
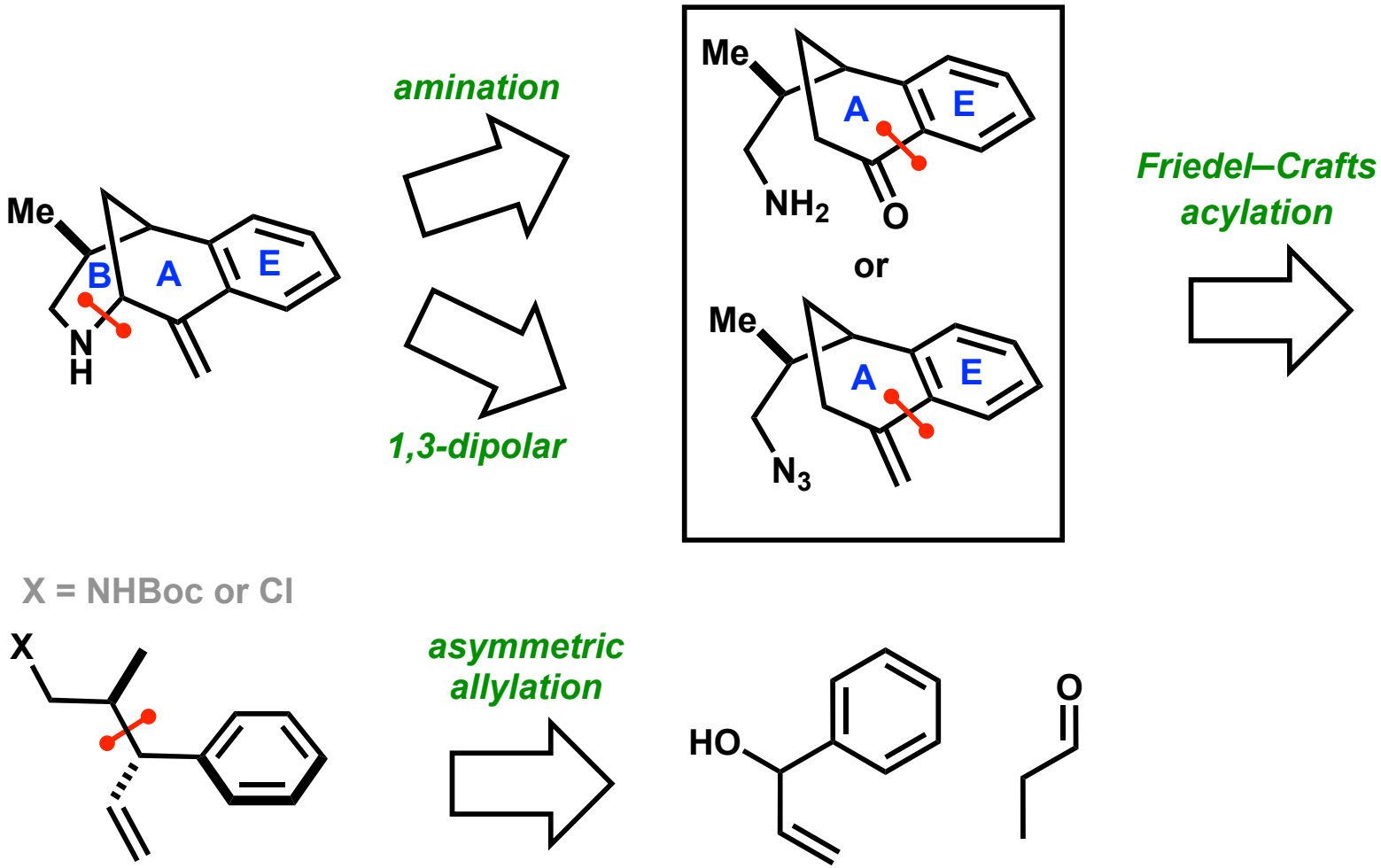
Retrosynthetic Analysis



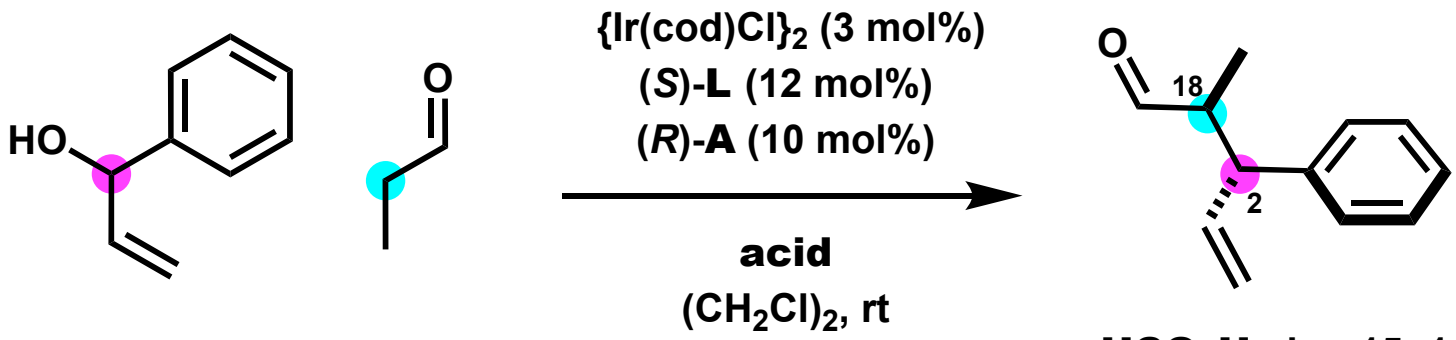
1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.

Retrosynthetic Analysis

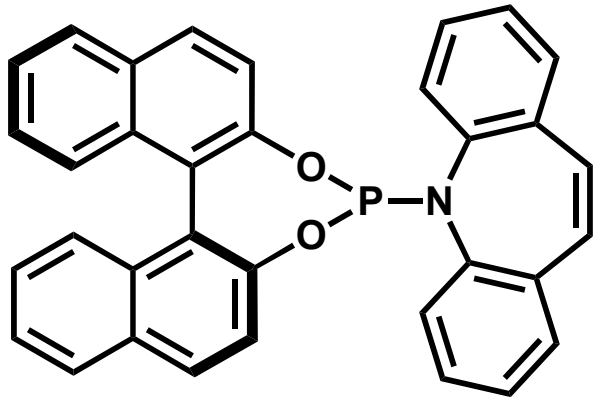


1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.

Ir / amine Dual-catalyzed Allylation

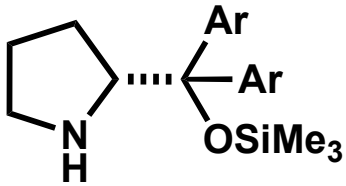


HCO_2H, dr = 15 :1
ee > 99%, yield 45%
Cl_2CHCO_2H, dr = 6:1
ee > 99%, yield 75%

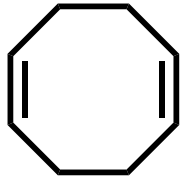


(*S*)-**L**

(Ar = 3,5-$(CF_3)_2$-Ph)



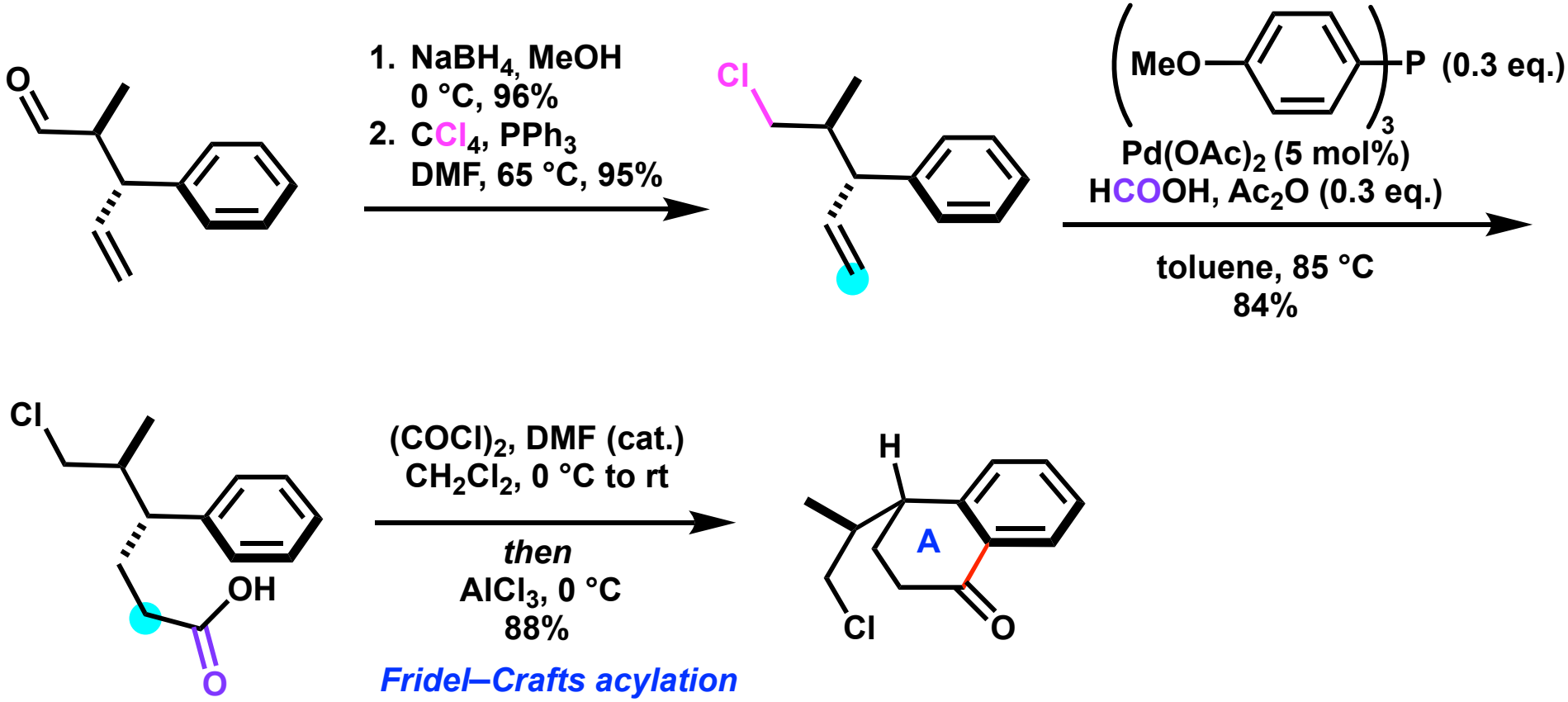
(*R*)-**A**



cod

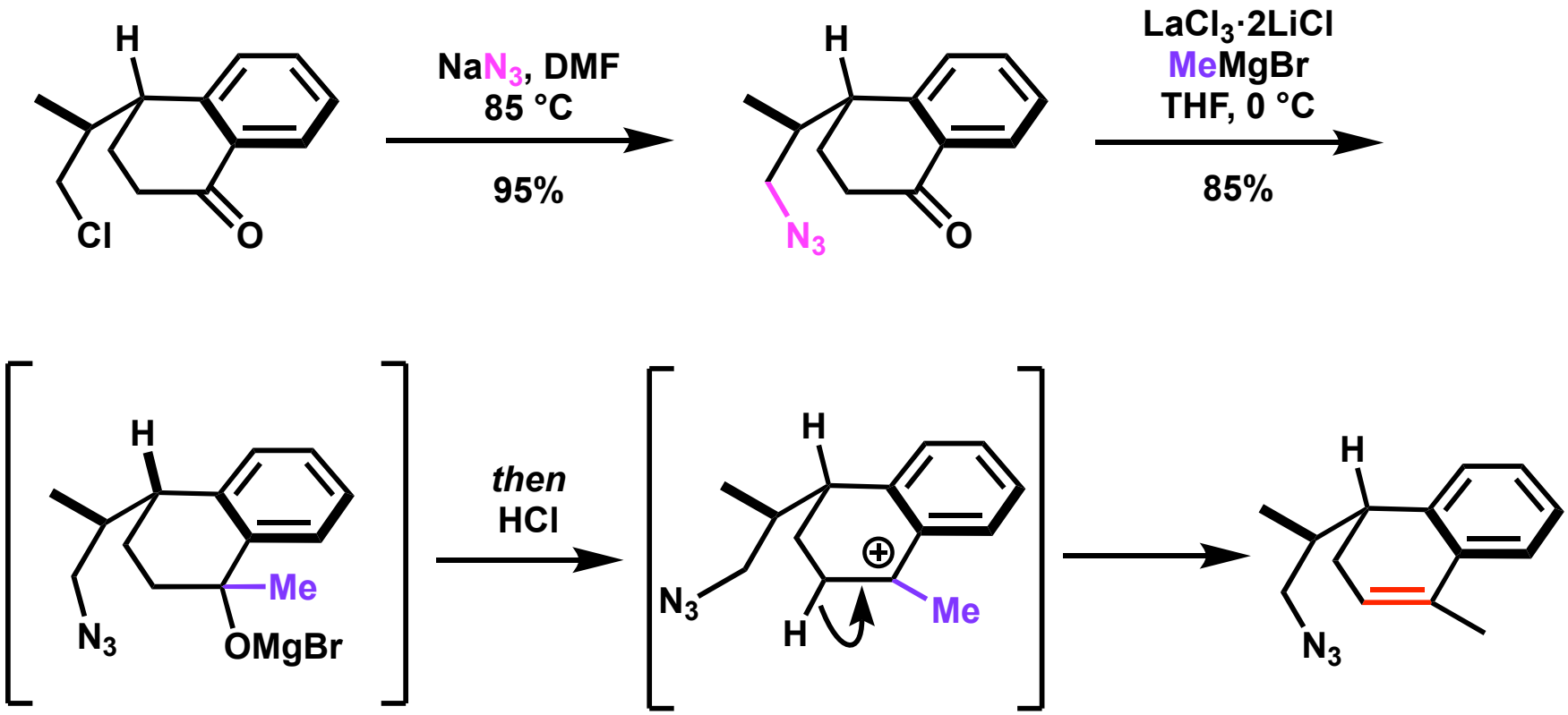
1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065-1068.

Chlorination and A-ring Construction



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Ren, W.; Chu, J.; Sun, F.; Shi, Y. *Org. Lett.* **2019**, *21*, 5967-5970.

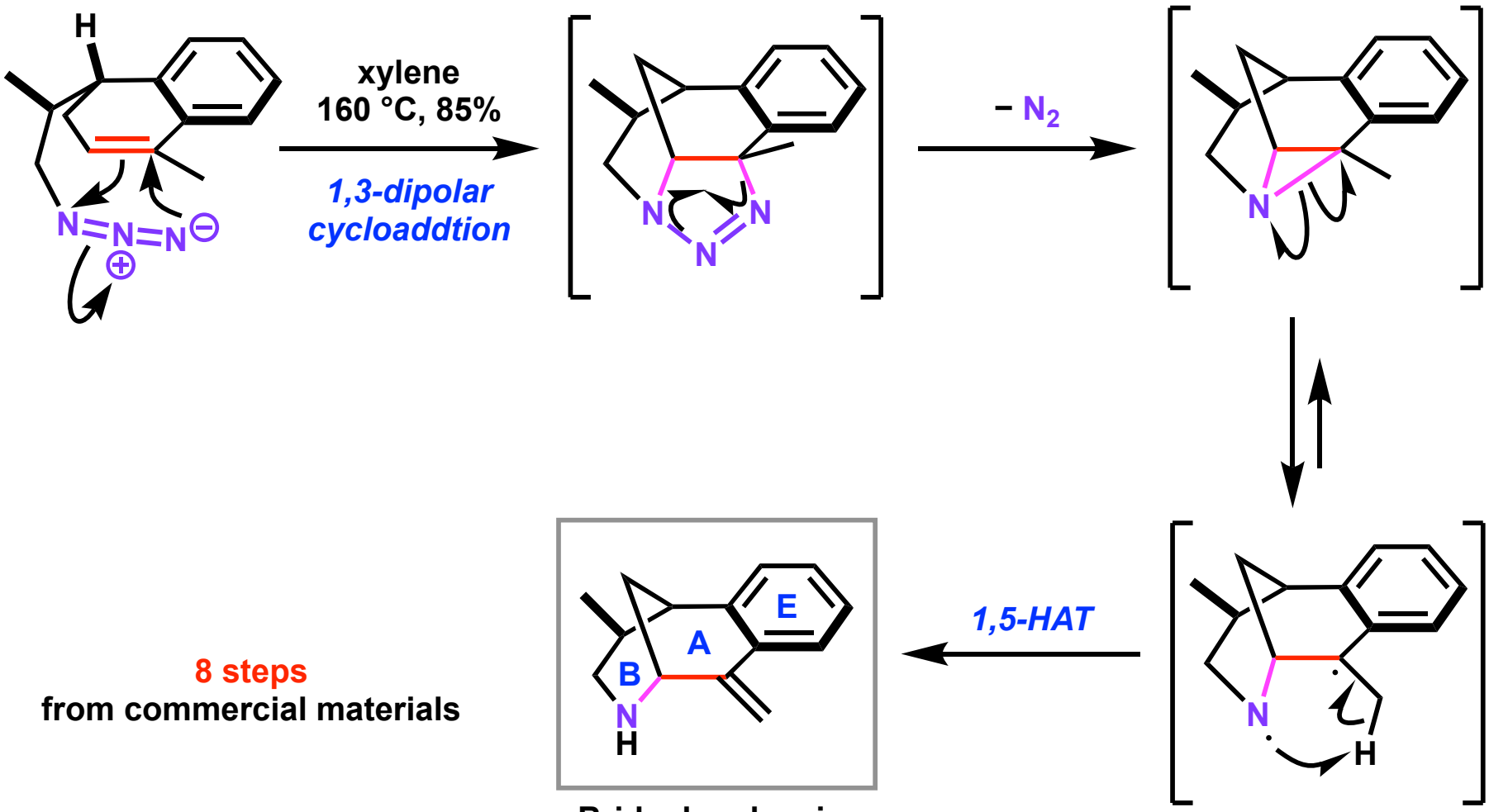
Azidation and Olefination



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.

1,3-Dipolar Cycloaddition

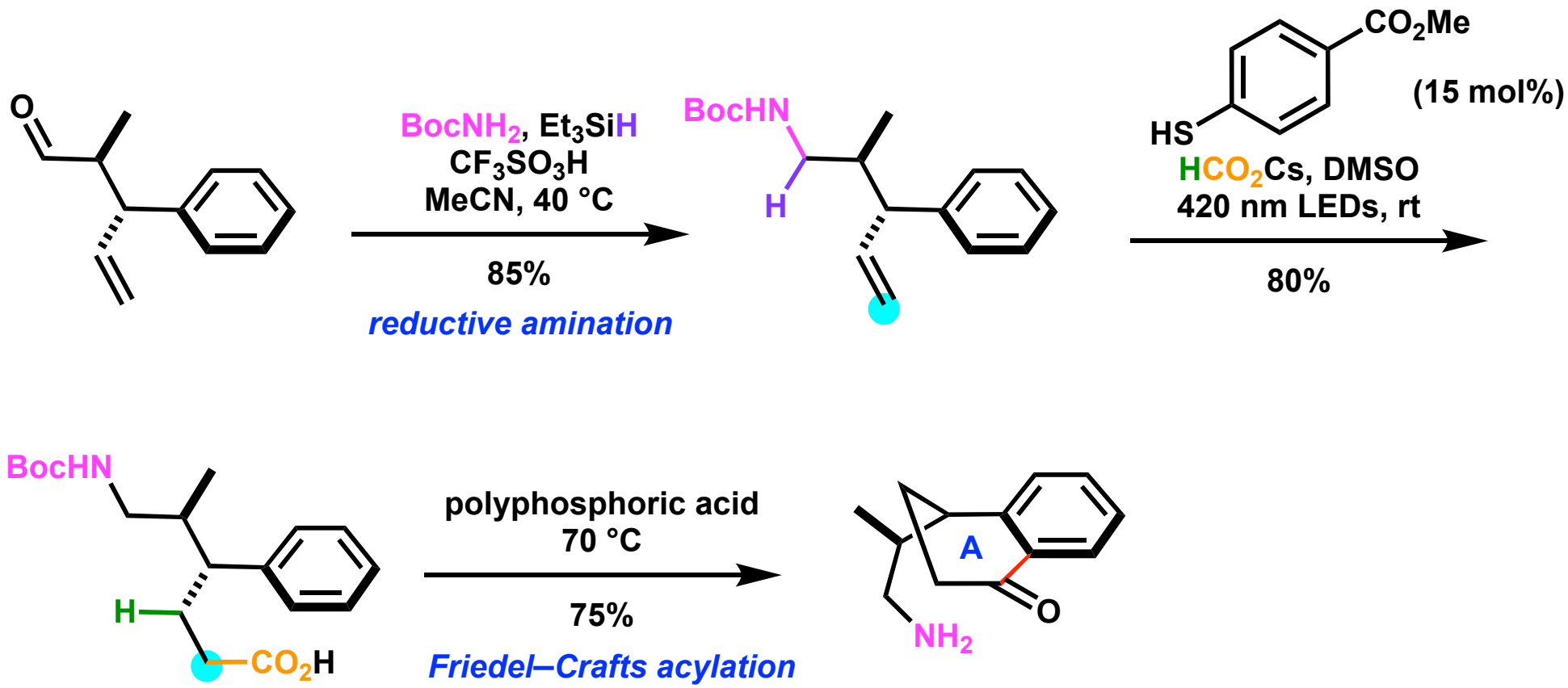
Reaction mechanism proposed by the authors



Bridgehead amine intermediate

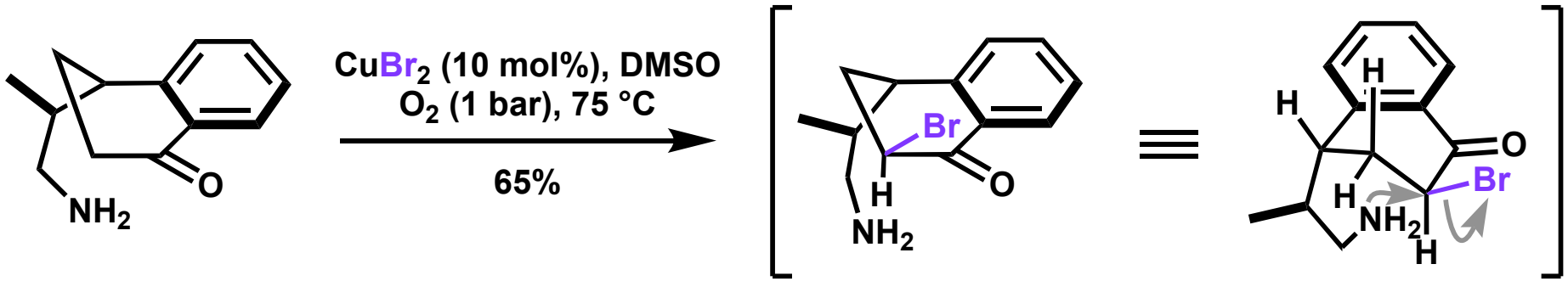
1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.

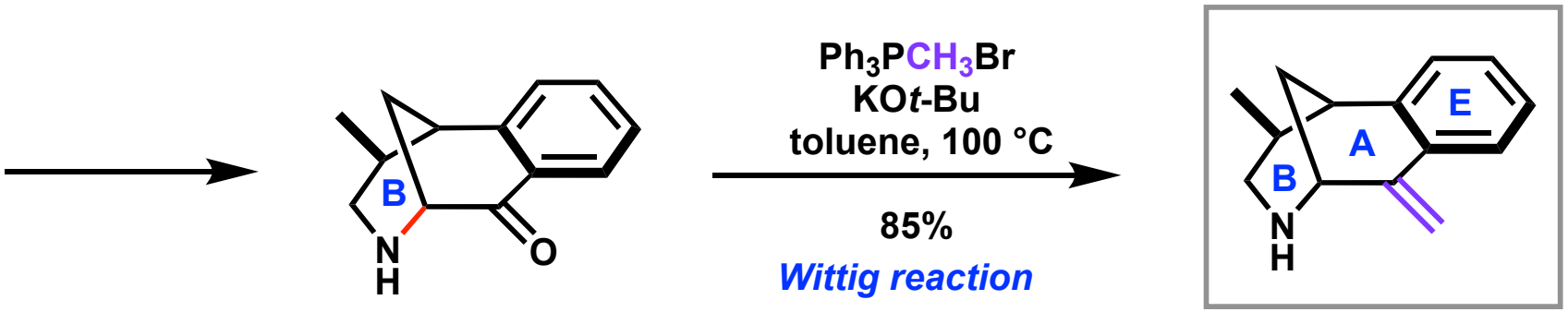
Second Route for Bridgehead Amine Intermediate



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Alektiar, S. N.; Han, J.; Dang, Y.; Rubel, C. Z.; Wickens, Z. K. *J. Am. Chem. Soc.* **2023**, *145*, 10991−10997.

Intramlecular α-Amination



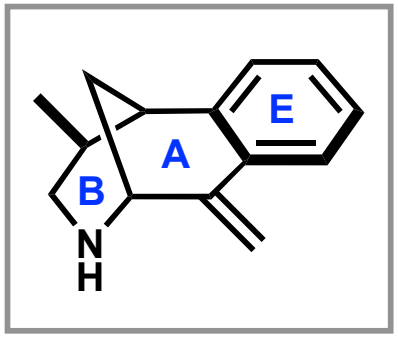


Bridgehead amine intermediate

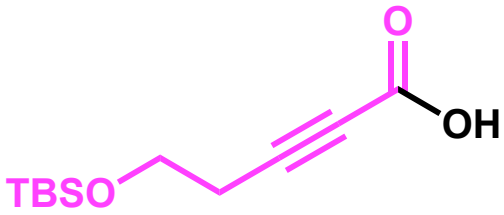
6 steps
from commercial materials

1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 16074−16077.

Amidation and C-ring Construction

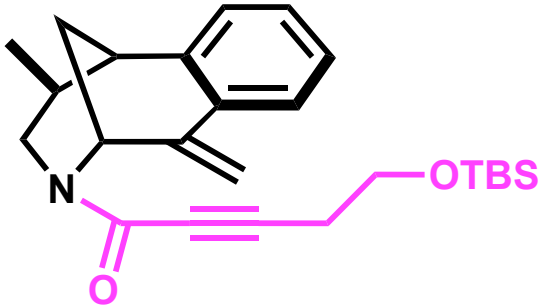


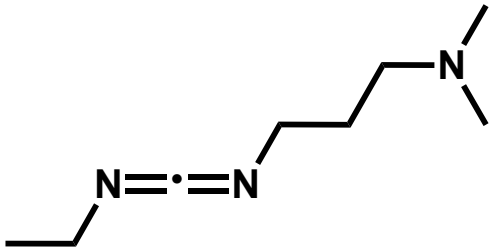
Bridgehead amine intermediate



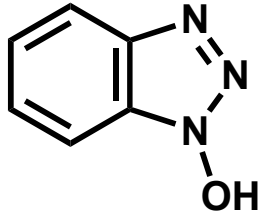
EDCI, HOBt, *i*-Pr_2NEt
CH_2Cl_2, 0 °C to rt

95%





EDCI



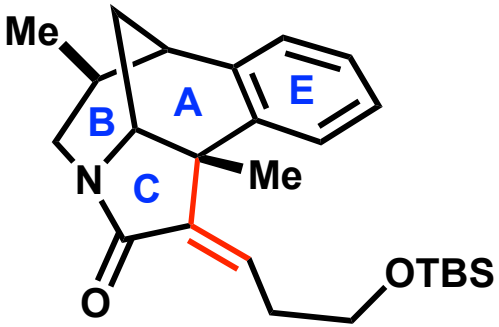
HOBt

iodination

Pd-catalyzed reductive Heck cyclization

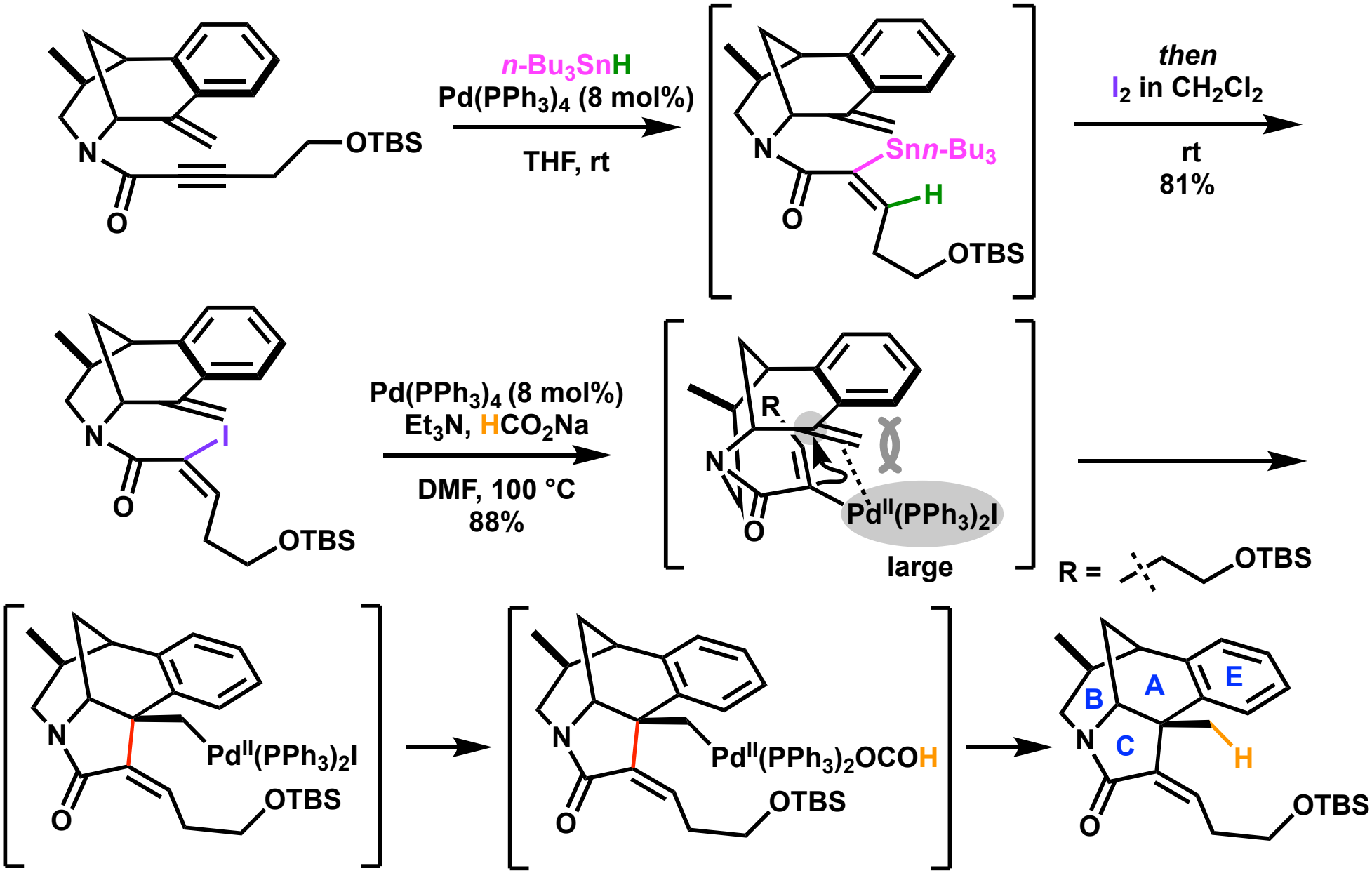
or

Rh-catalyzed reductive 1,6-enyne cyclization



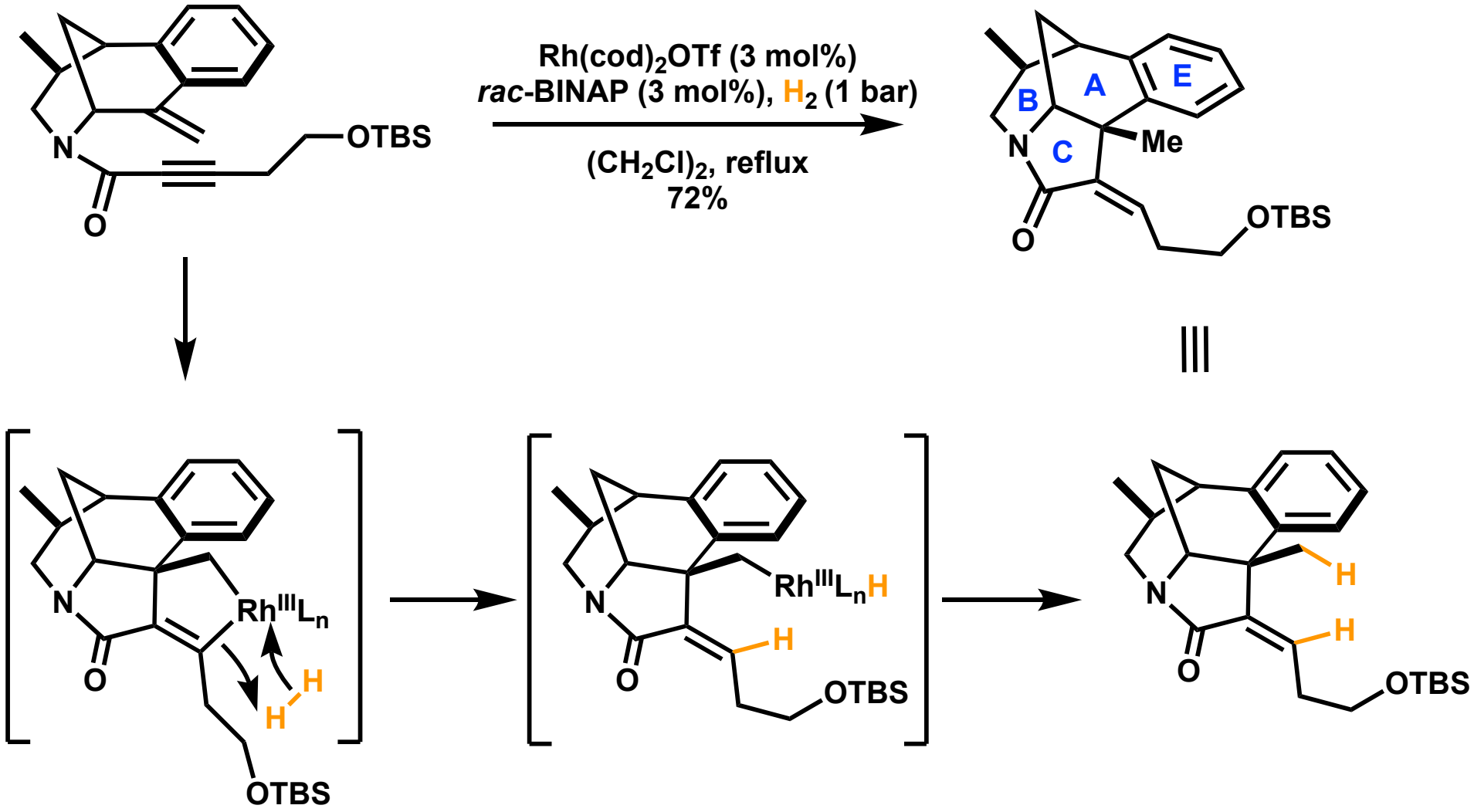
1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Carey, J. S. *J. Org. Chem.* **2001**, *66*, 2526−2529.

Reductive Heck Reaction



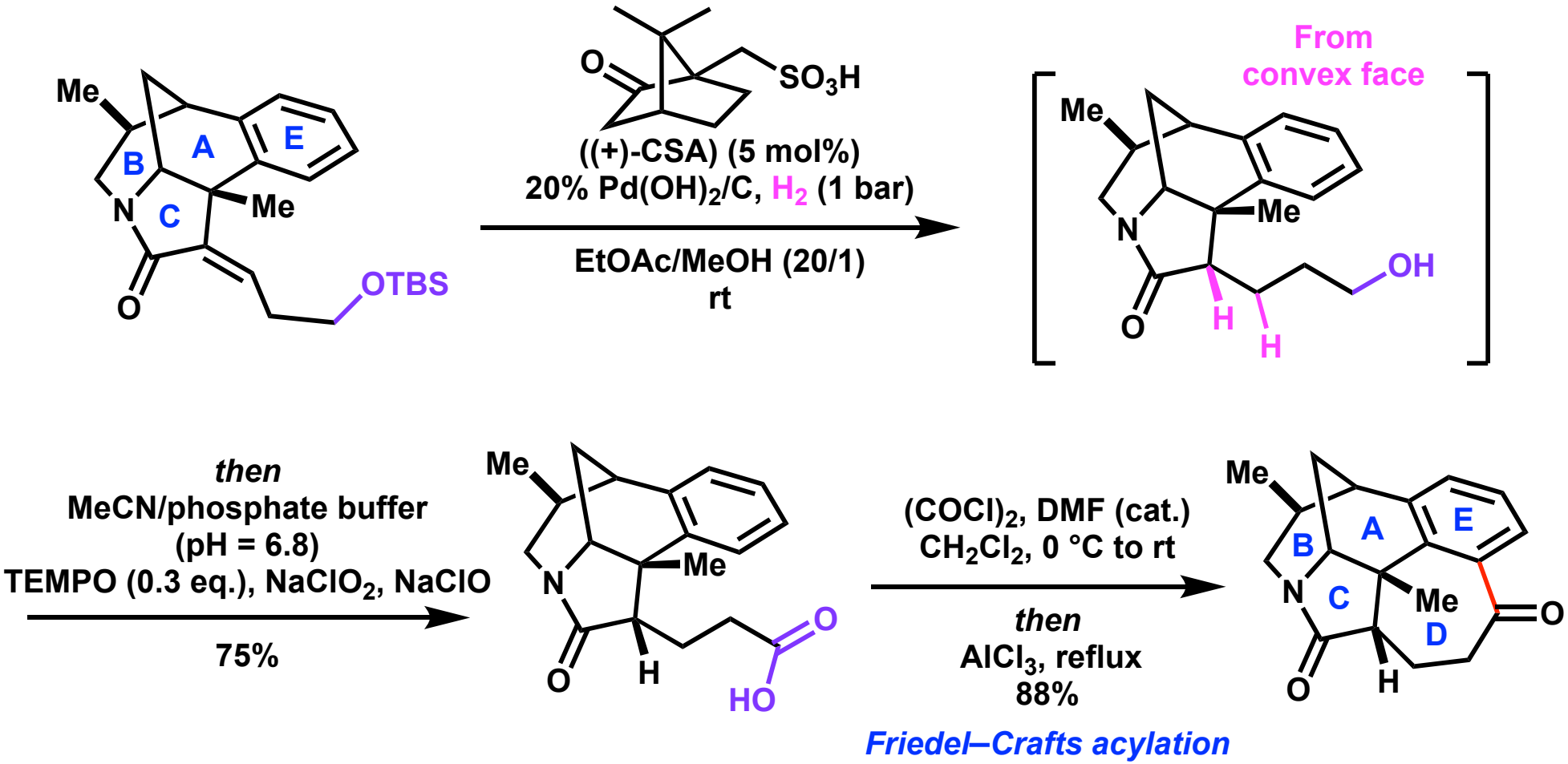
1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Bellina, F.; Carpita, A.; Ciucci, D.; De Santis, M.; Rossi, R. *Tetrahedron* **1993**, *49*, 4677−4698.
3) Ghosh, T. *Chemistry Select* 2**019**, *4*, 4747−4755.

Reductive Enyne Cyclization



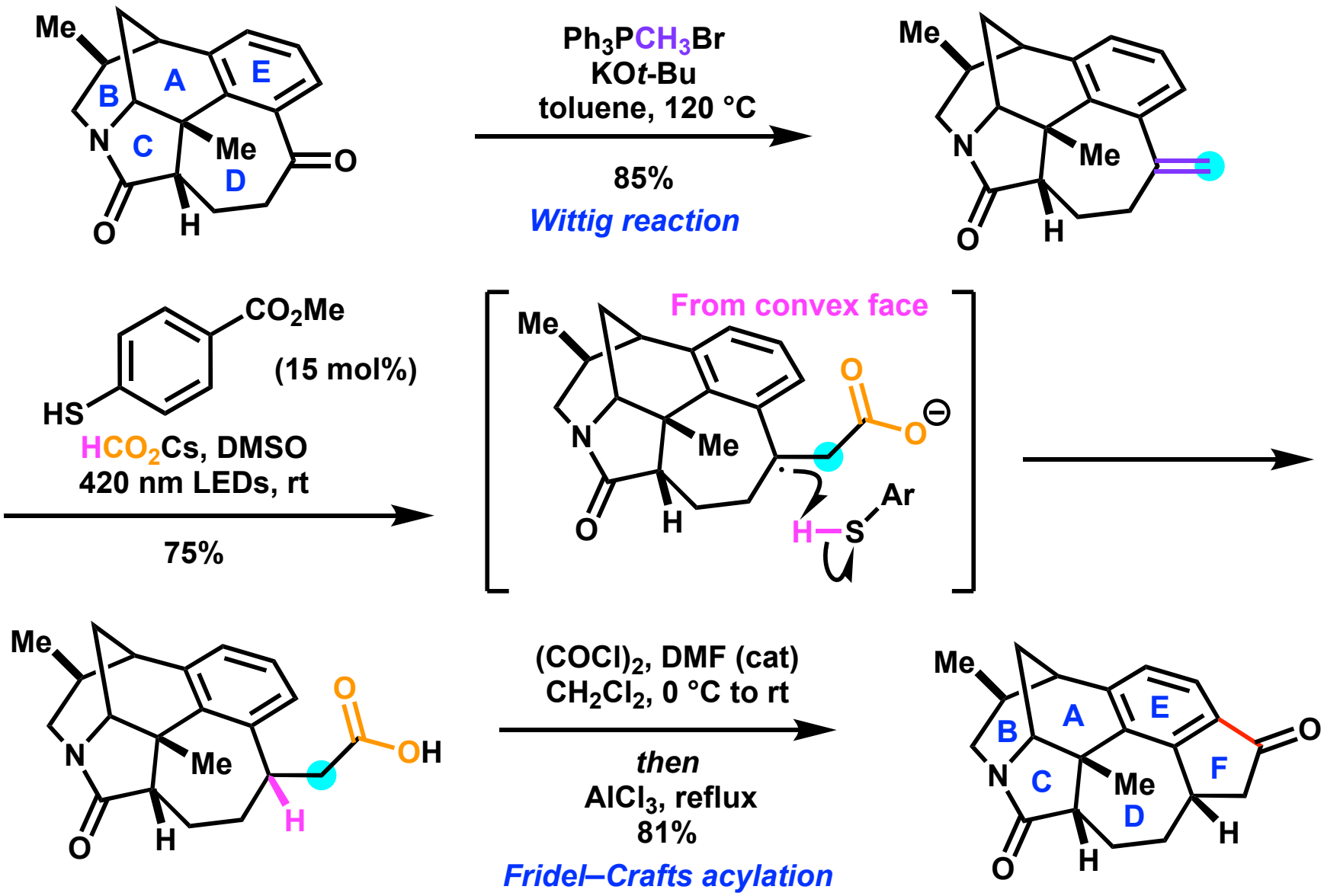
1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Jang, H.-Y.; Hughes, F. W.; Gong, H.; Zhang, J.; Brodbelt, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 6174−6175.

D-ring Construction



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564−2566.

F-ring Construction



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
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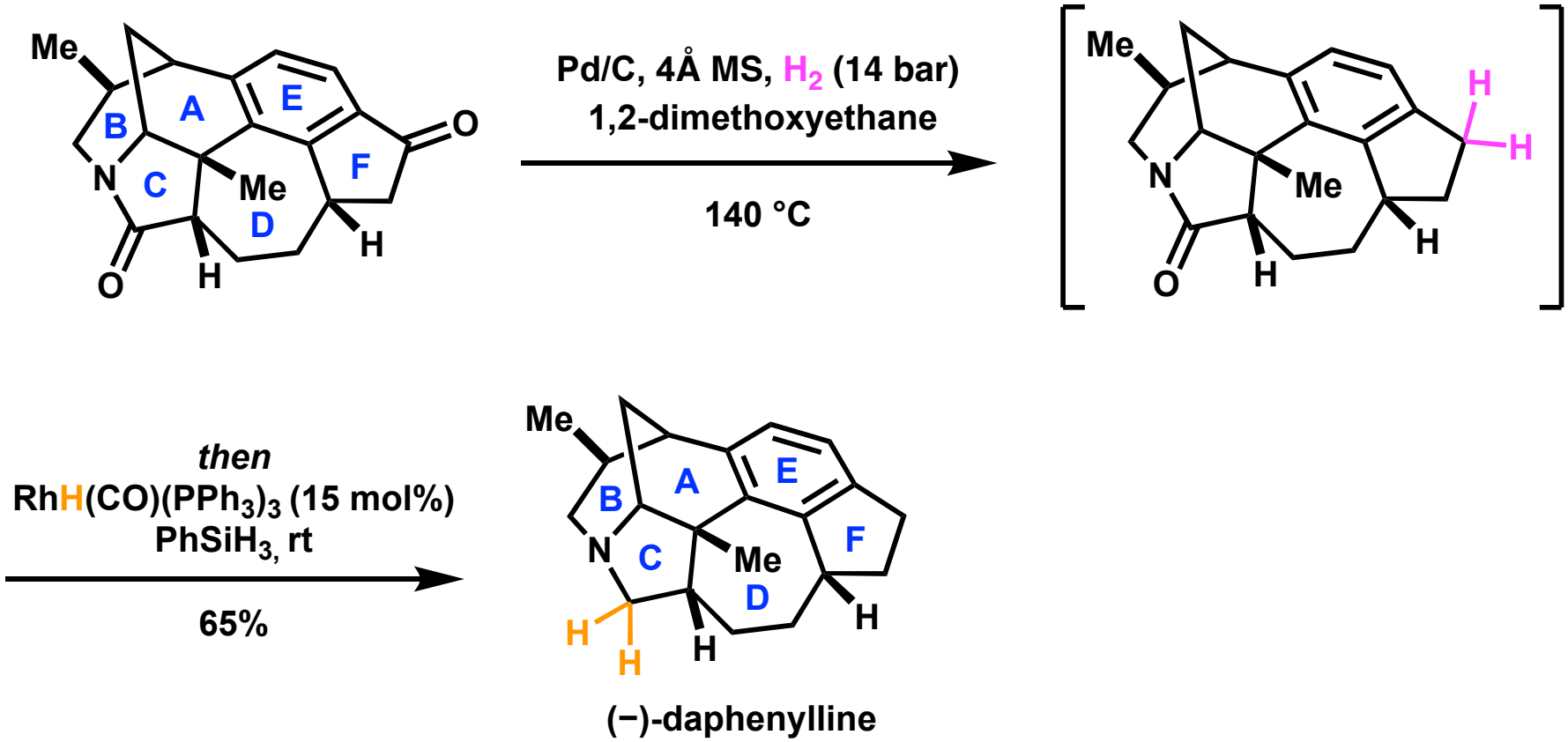
Total Synthesis of (−)-Daphenylline



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017−1020.

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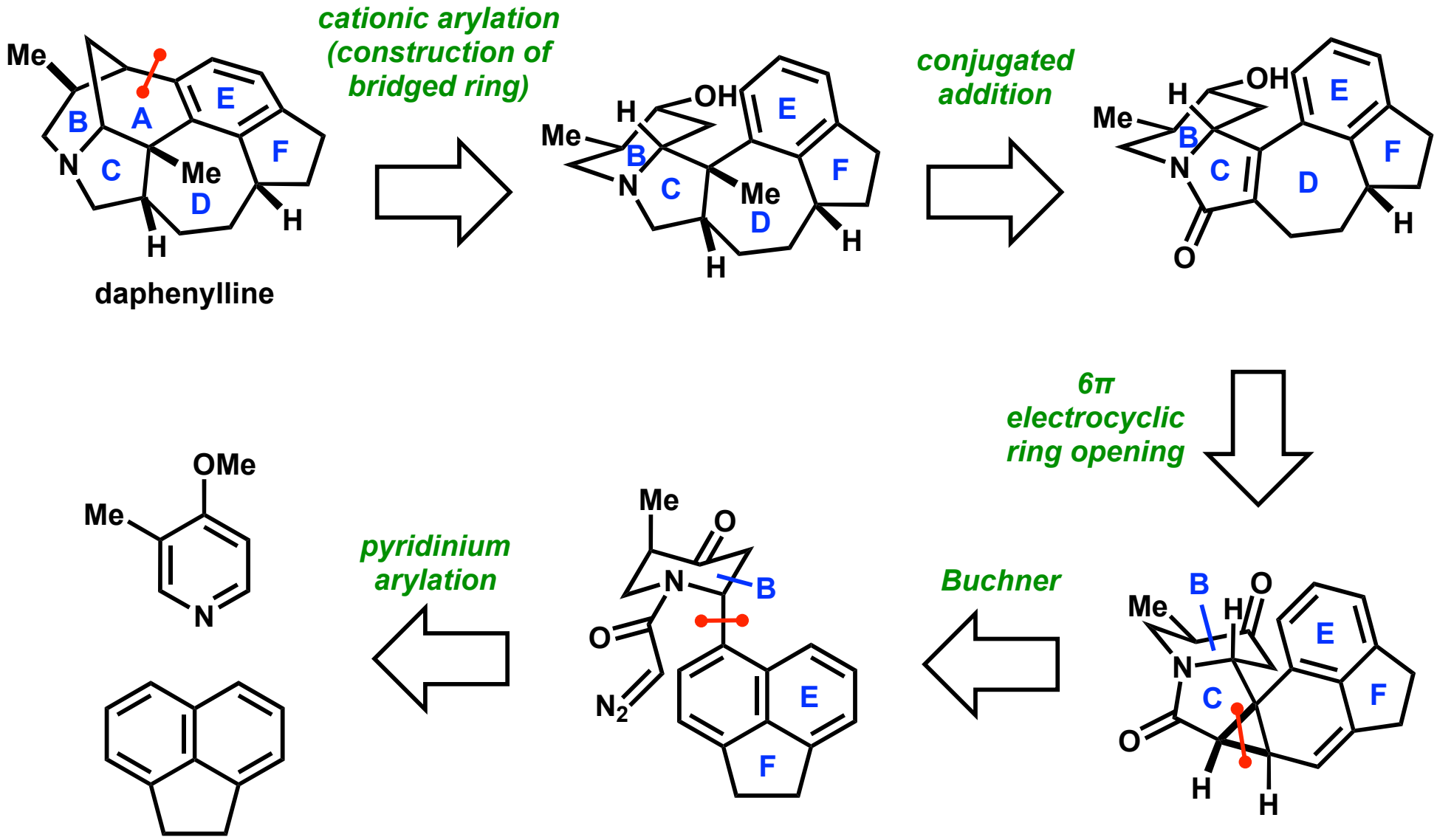
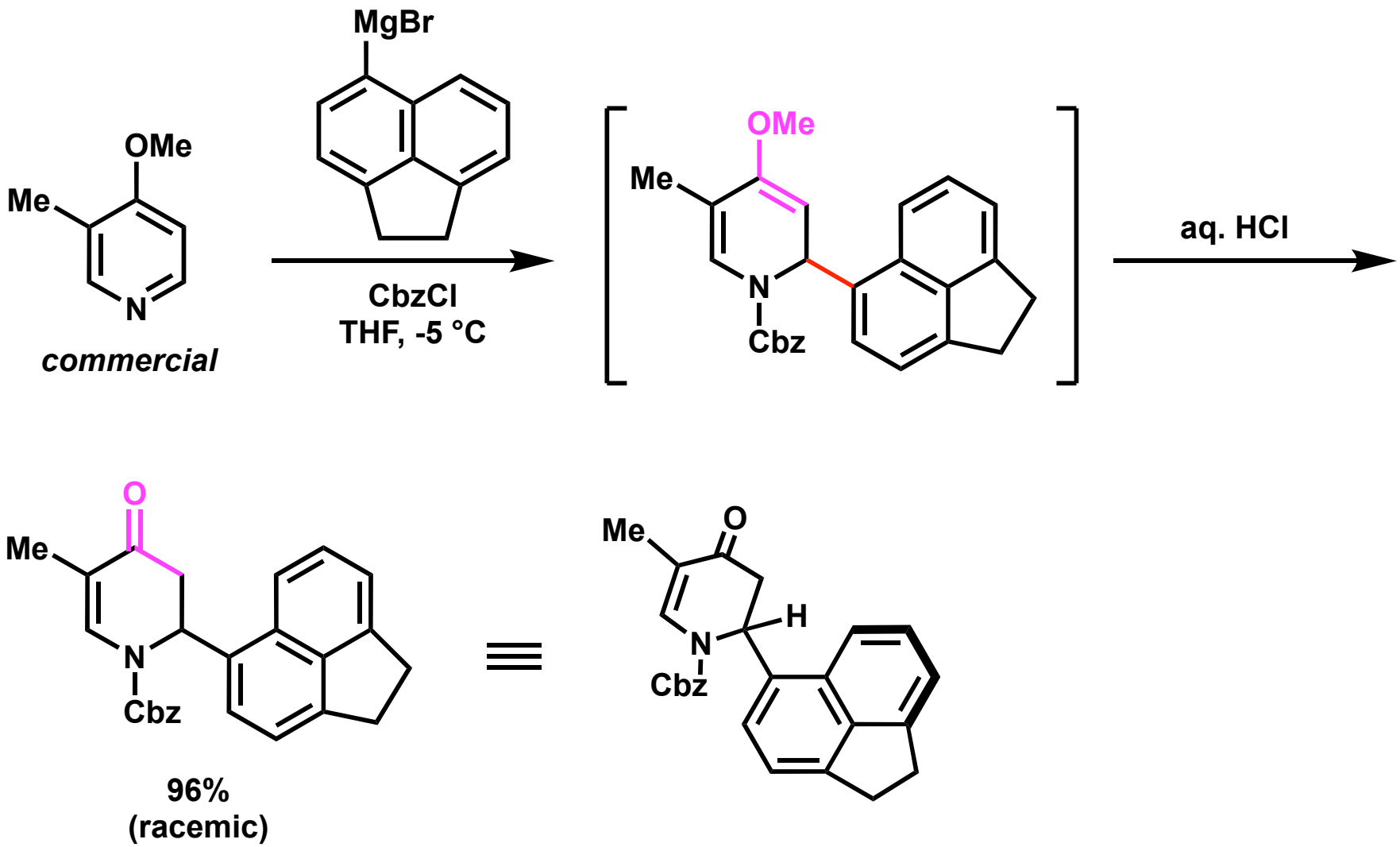
Retrosynthetic Analysis



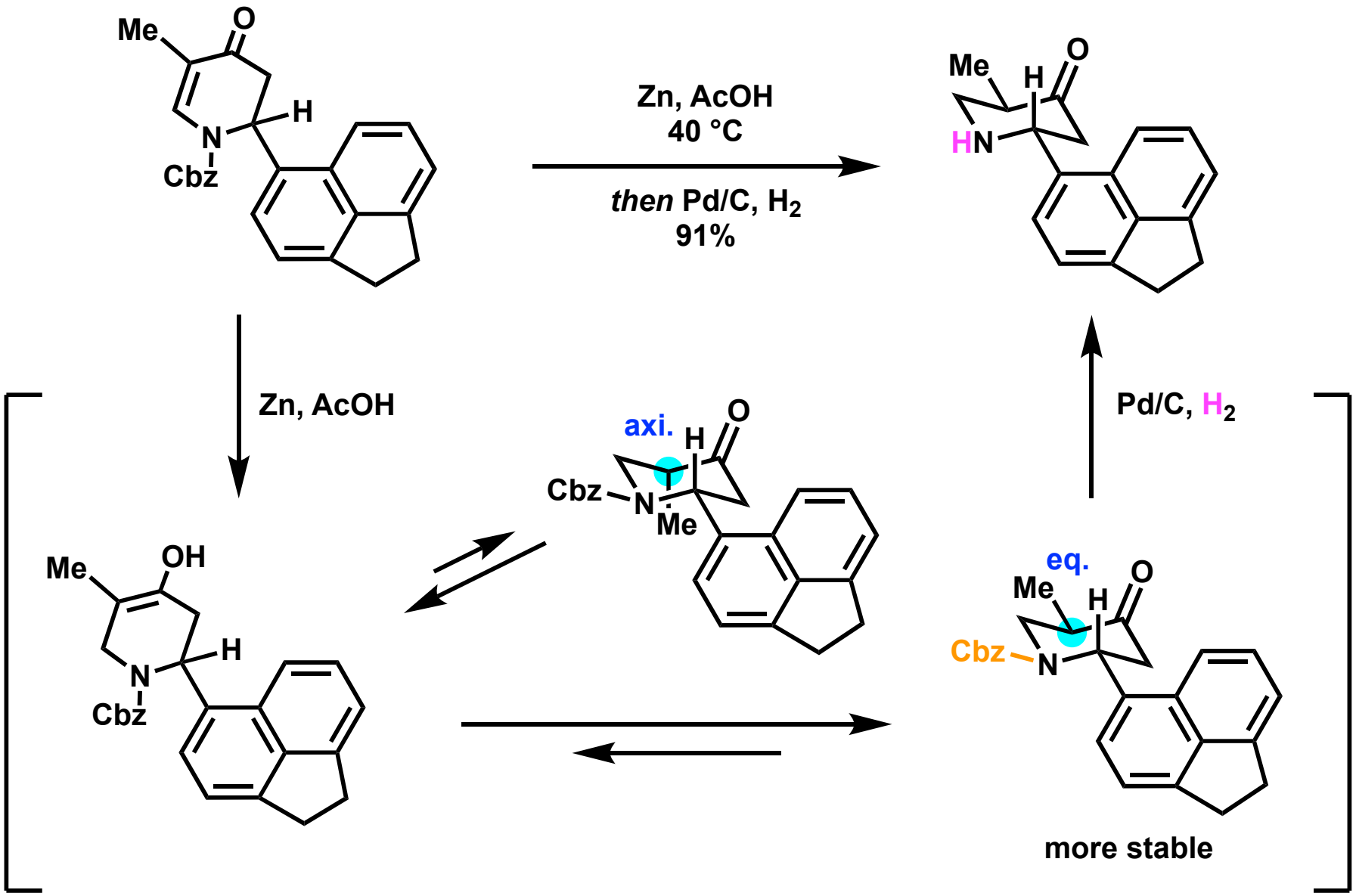
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

Pyridinium Arylation



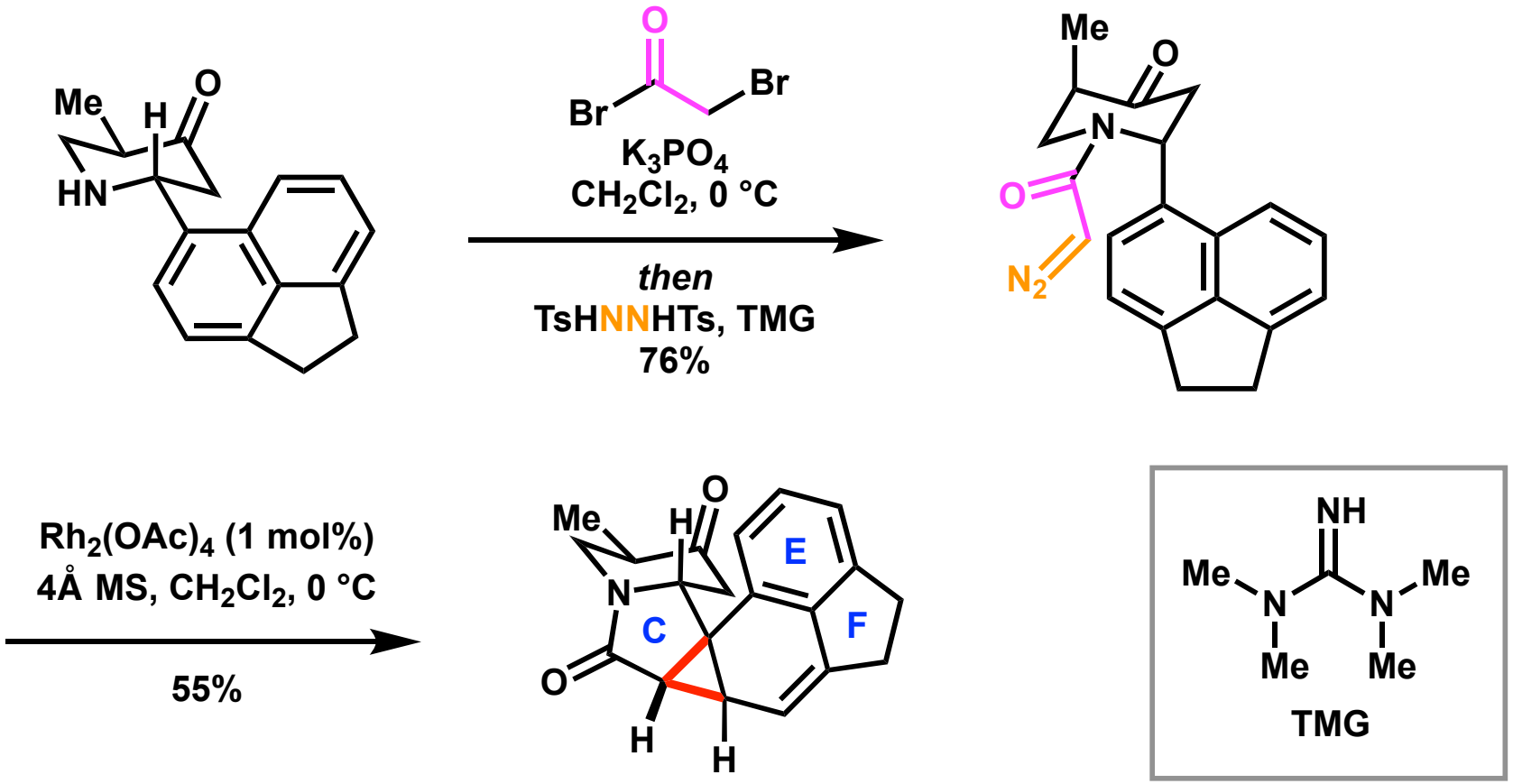
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

Reduction of Dihydropyridone with Zinc



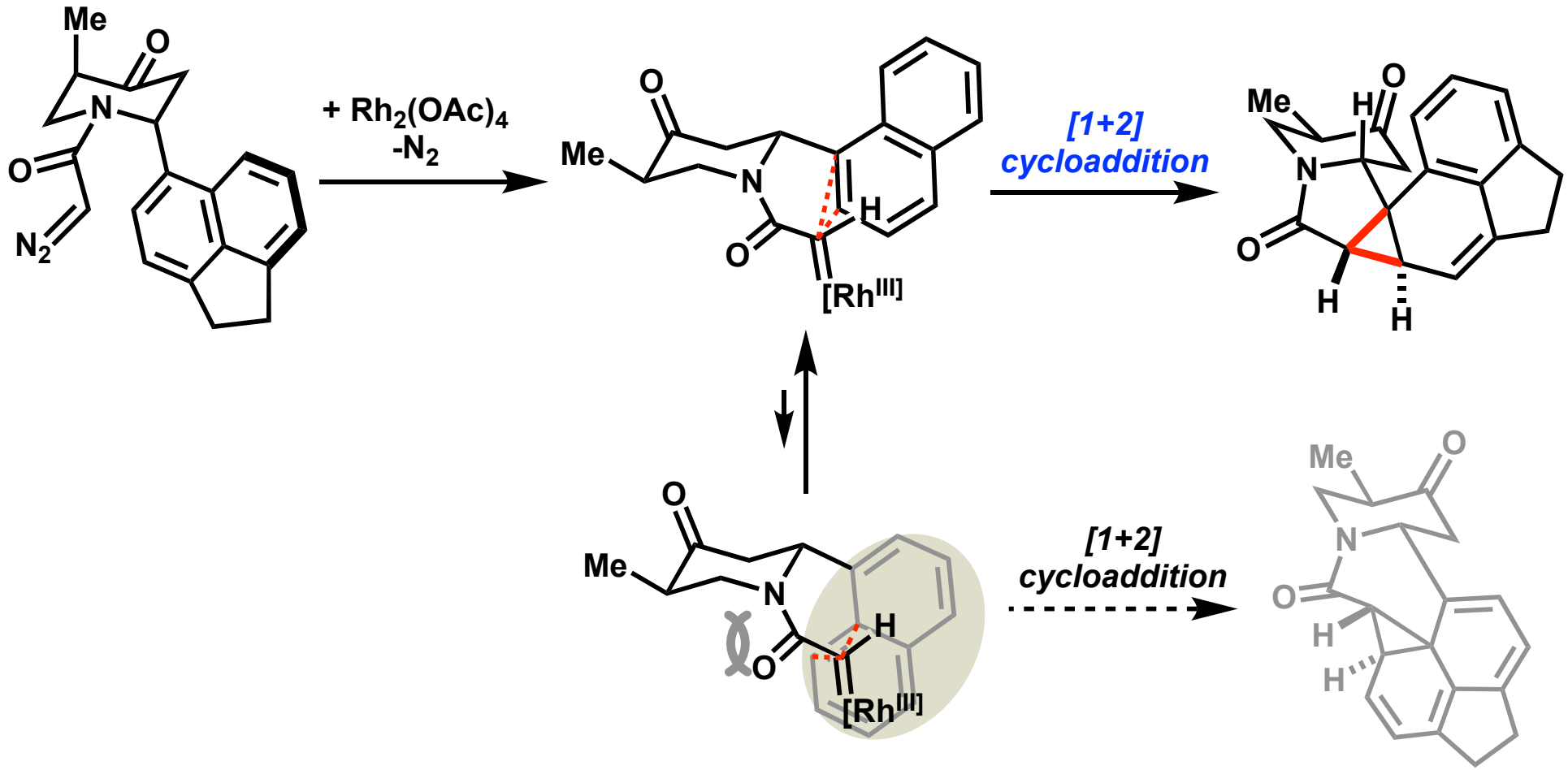
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.
2) Comins, D. L.; Brooks, C. A.; Ingalls, C. L. *J. Org. Chem.* **2001**, *66*, 2181−2182.

Intramolecular Buchner Reaction



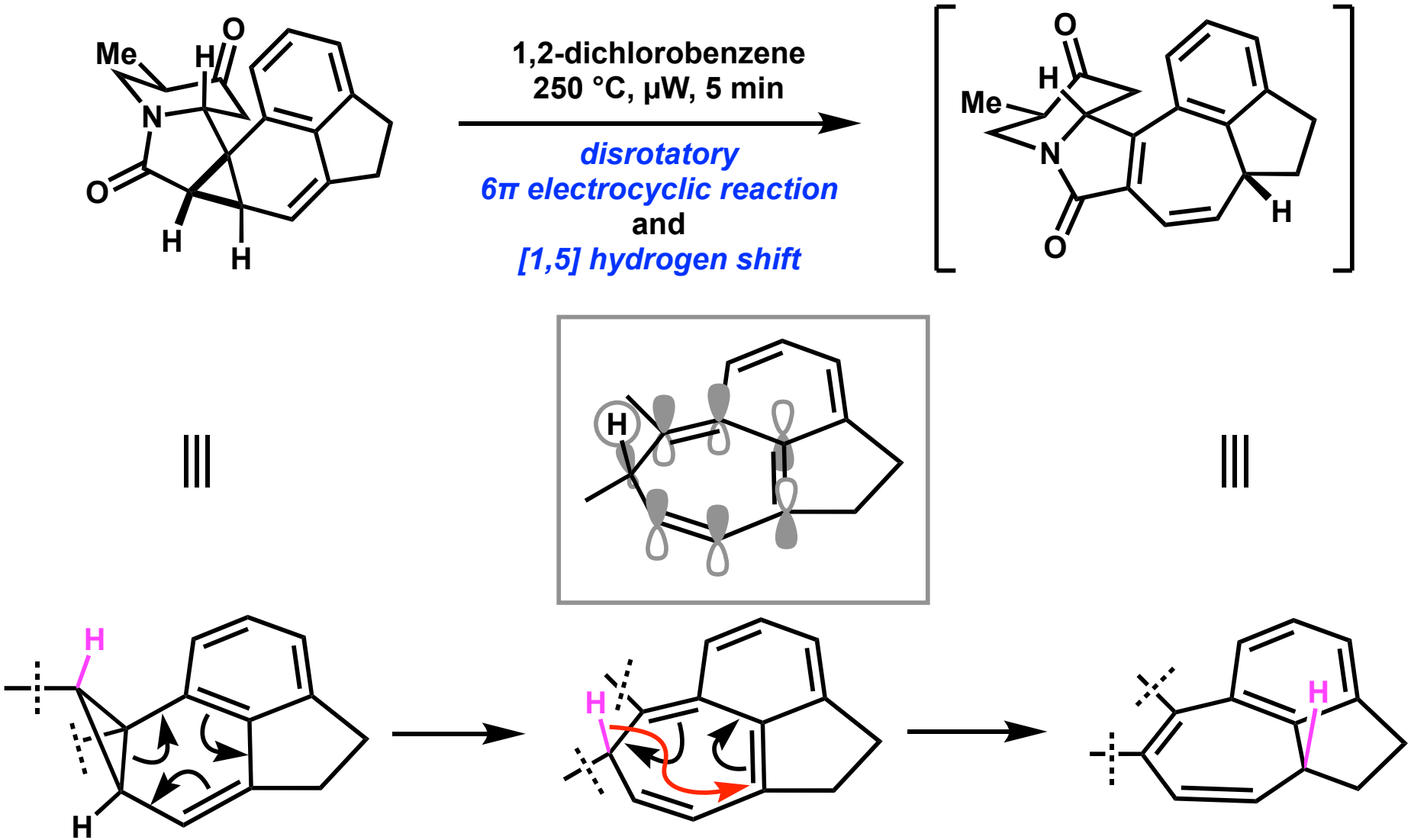
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.
2) Toma, T.; Shimokawa, J.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 3195−3197.
3) Kaupang, A.; Bonge-Hansen, T. *Beilstein J. Org. Chem.* **2013,** *9*, 1407−1413.

Regioselectivity Buchner Reaction



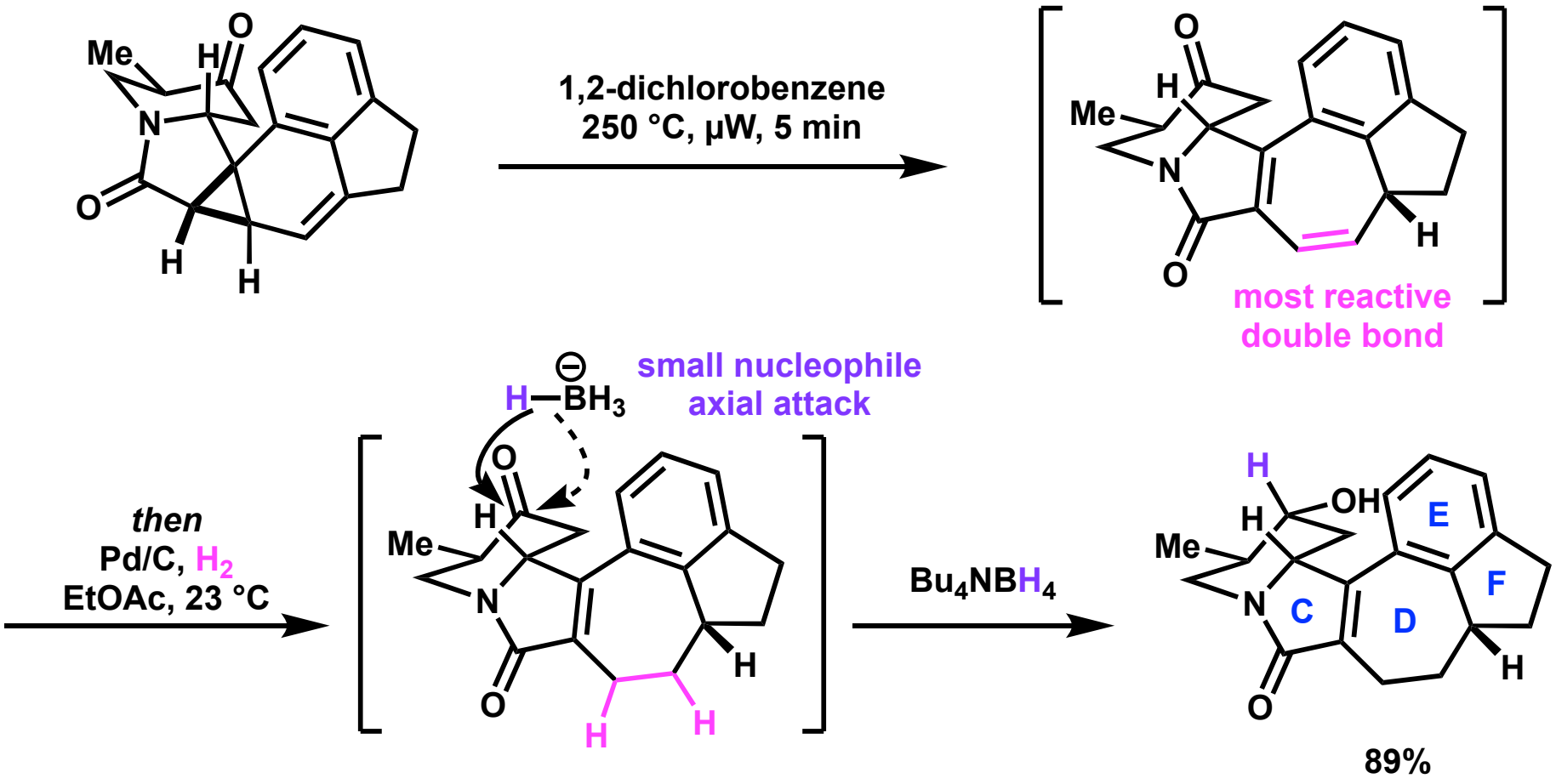
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

6π-electrocyclic Reaction and [1,5] Hydrogen Shift



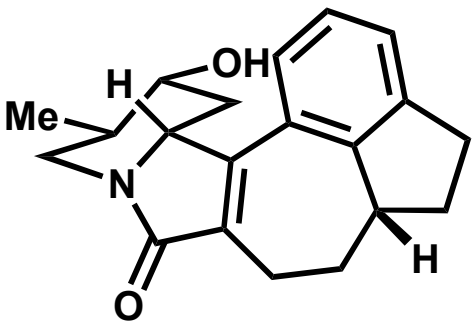
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.
2) Huisgen, R.; Juppe, G. *Chem. Ber.* **1961** ,*94*, 2332−2349.

Reduction



1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

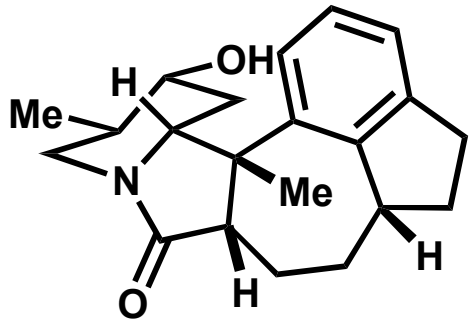
Attempted 1,4-Addition to Unsaturated Lactam



Methyl nucleophiles
- Gilman reagents (Me_2CuLi)
- Me_3Al / $Ni(acac)_2$

Methyl radical source
- PhthN-OAc / Ir^{III}

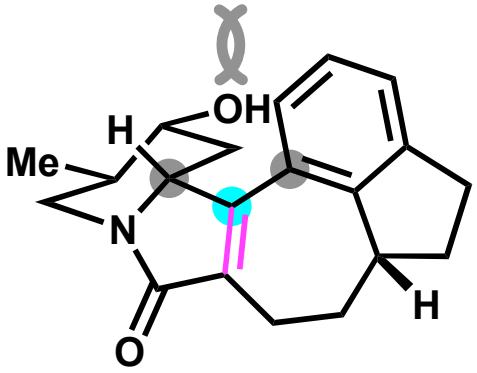
Methyl surrogates
- Nagata's reagent (Et_2AlCN)
- 1,3-dithianes
- Corey-Chaykovsky cyclopropanation



competitive reaction with ketone
or
nonspecific decomposition

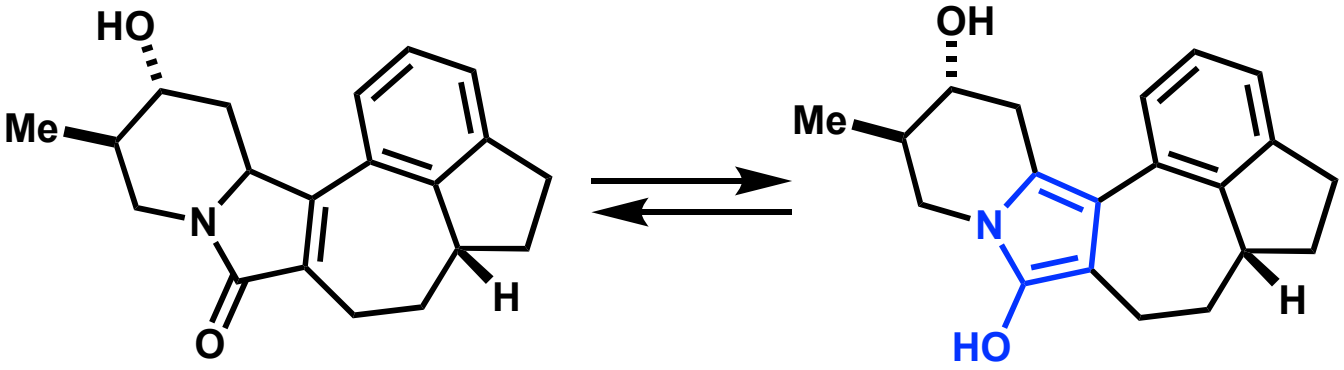
α,β-unsatulated lactam remained due to (proposed by the authors)

- Steric hinderance



tetrasubstituted alkene

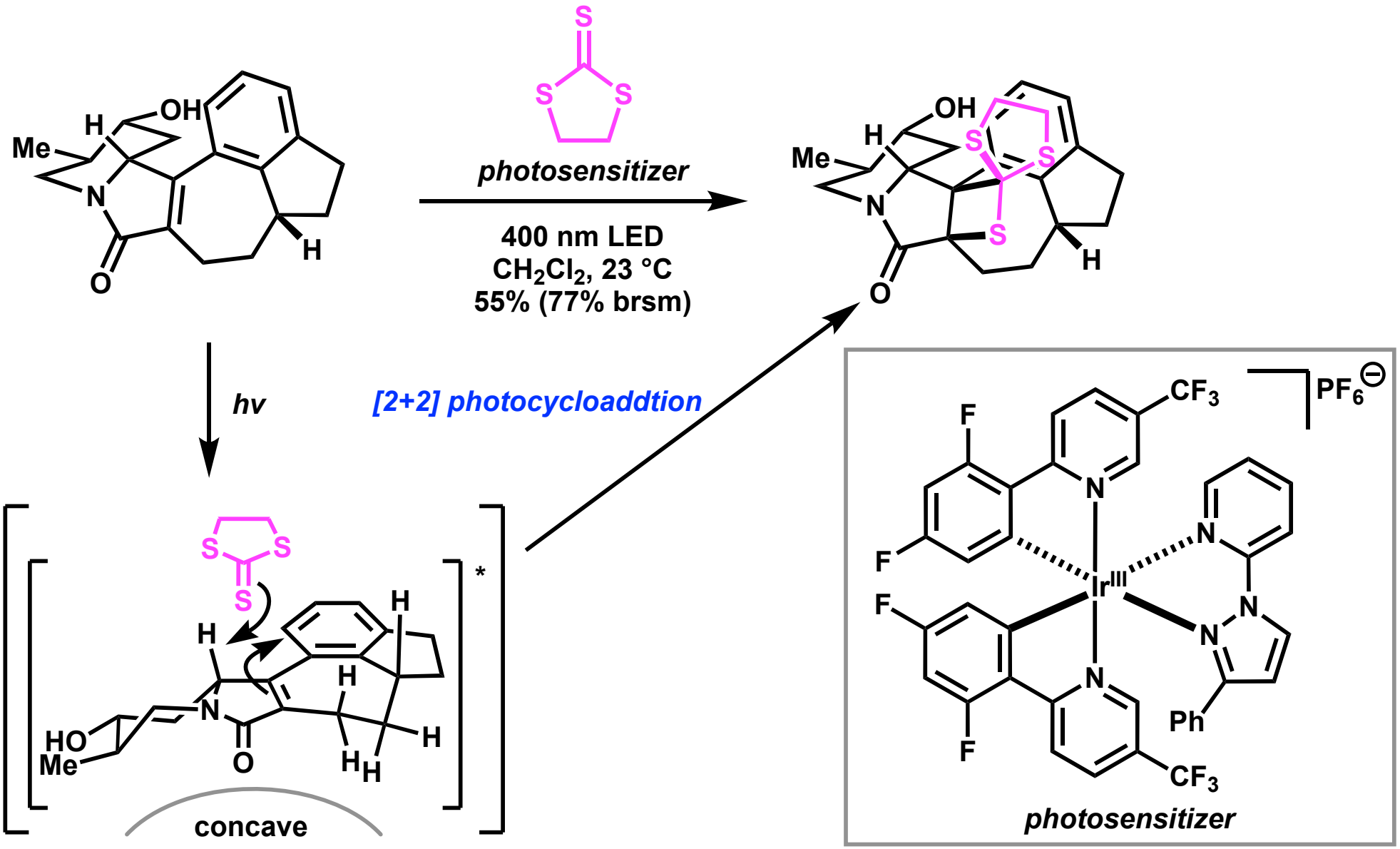
- Deactivation through tautomerization



2-hydroxypyrroles

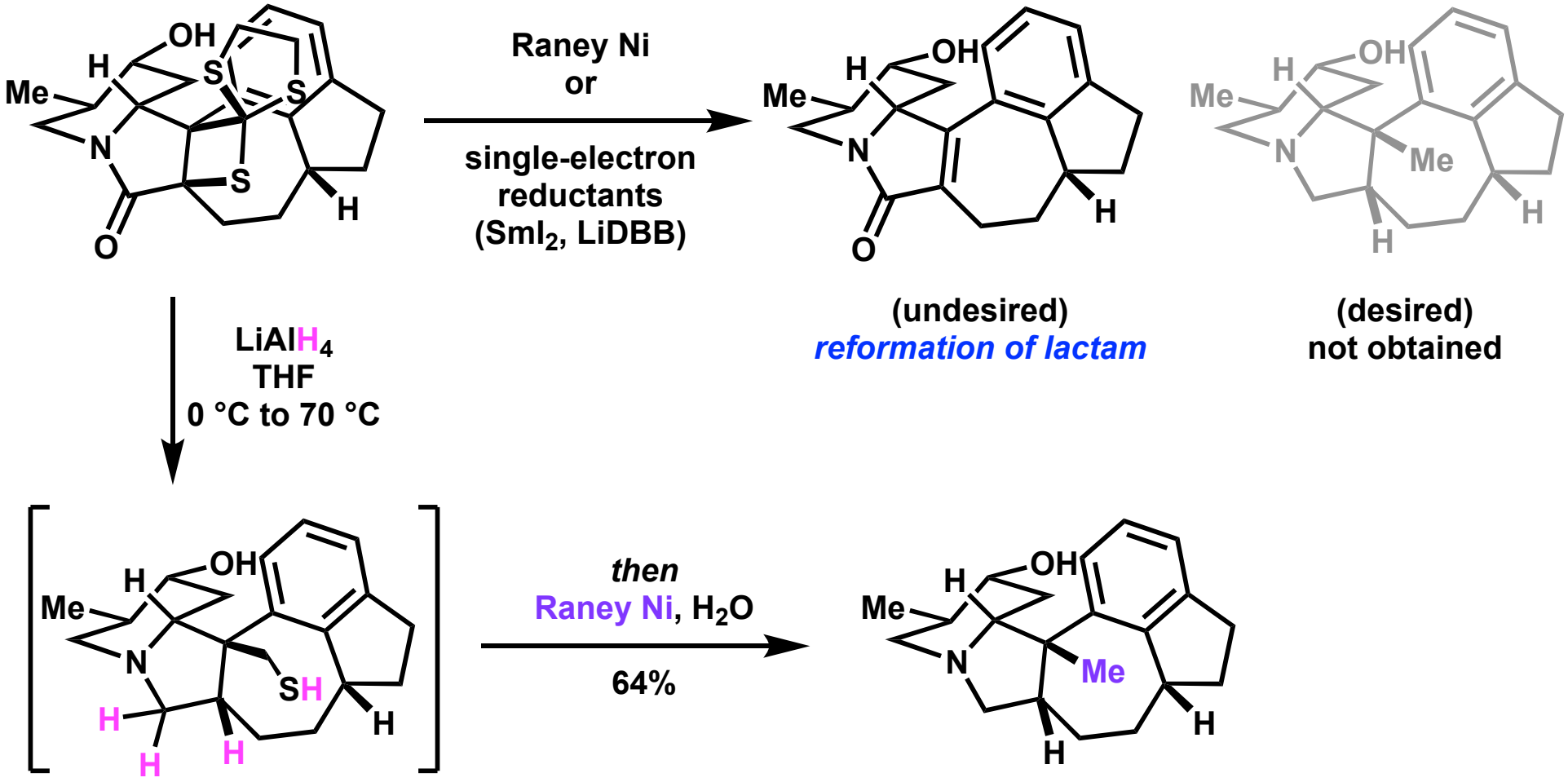
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

[2+2] Photocycloaddition



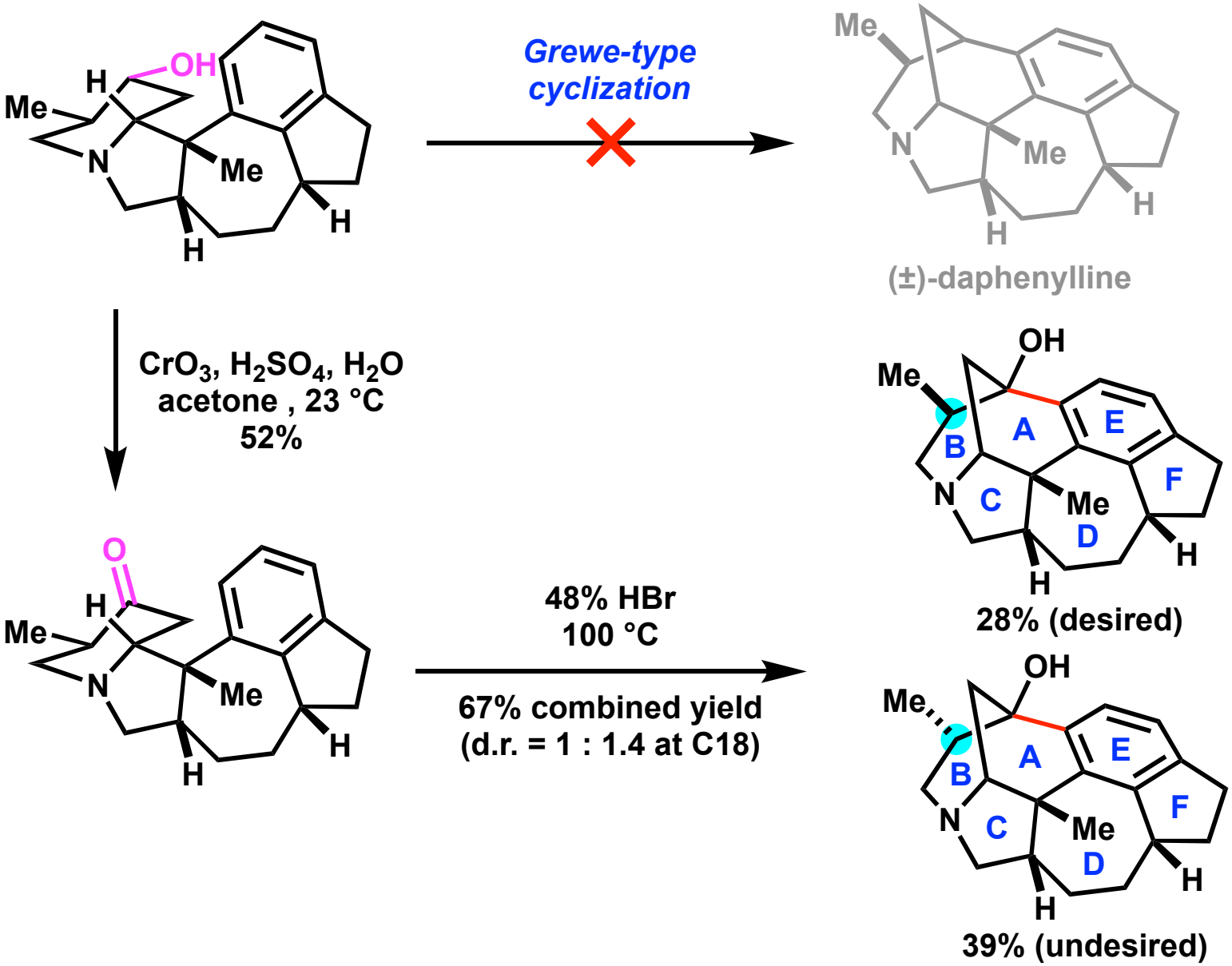
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.
2) Welin, E. R.; Le, C.; Arias-Rotondo, D.M.; McCusker, J.K.; MacMillan, D. W. C. *Science*, **2017**, *355*, 380-385.

Desulfurization



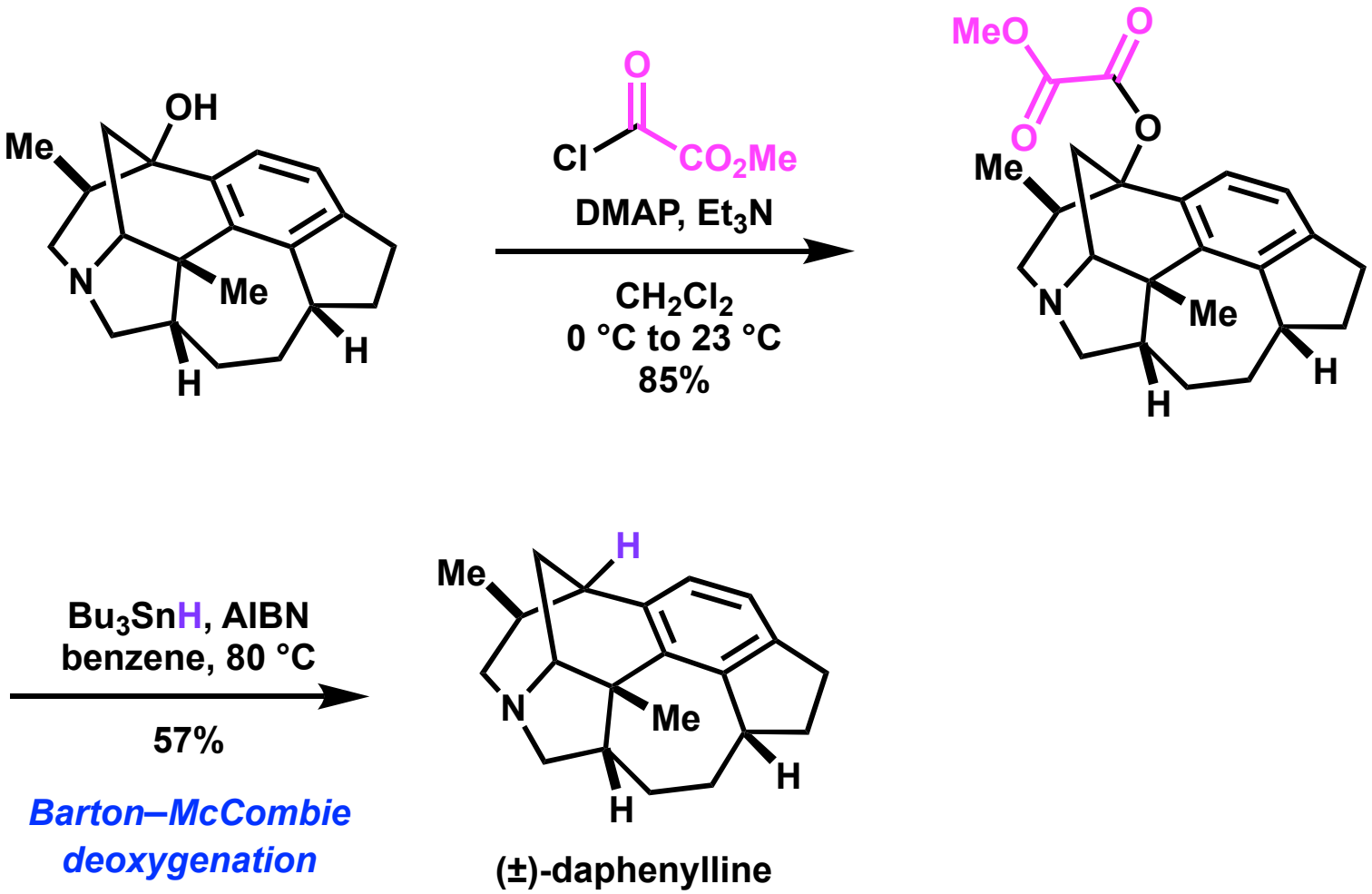
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

Bridged Ring Construction



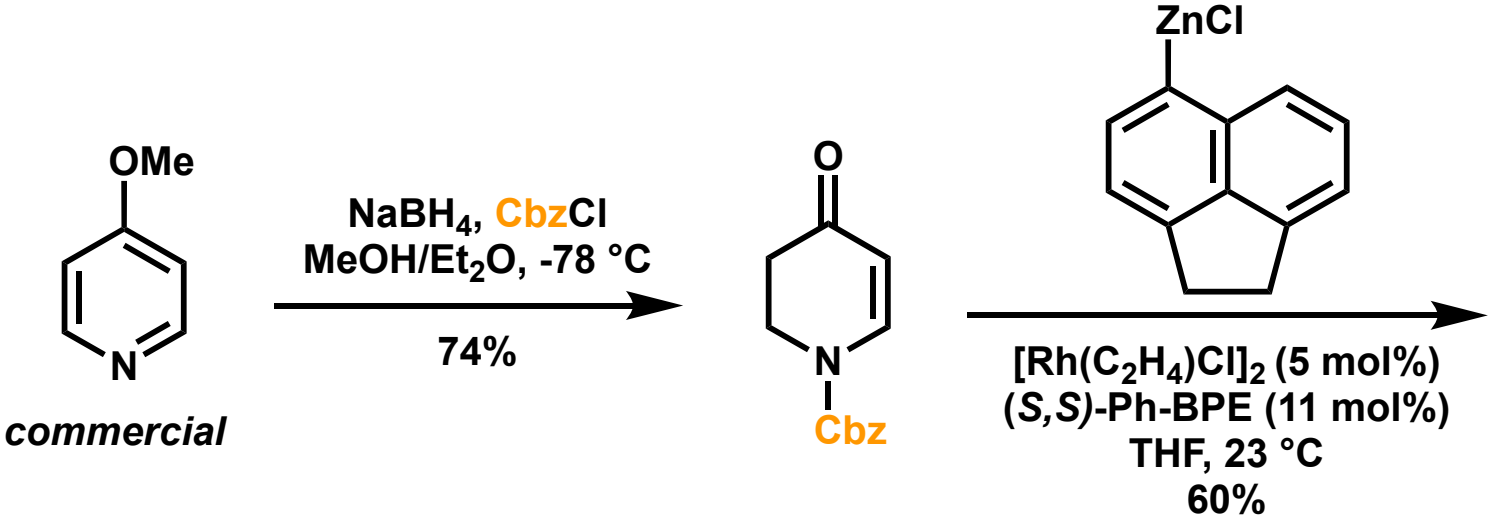
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

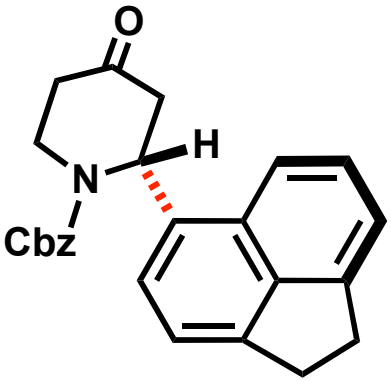
Total Synthesis of (±)-Daphenylline



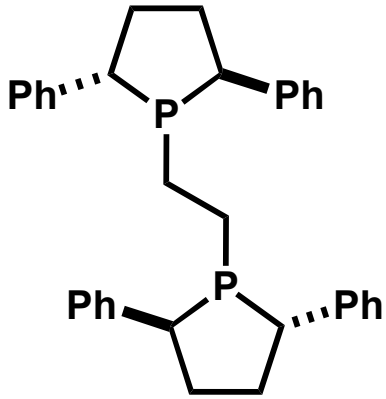
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.
2) Dolan, S. C.; MacMillan, J. *J. Chem. Soc., Chem. Commun.* **1985**, *22*, 1588−1589.

Enantioselective 1,4-addition for asymmetric Synthesis





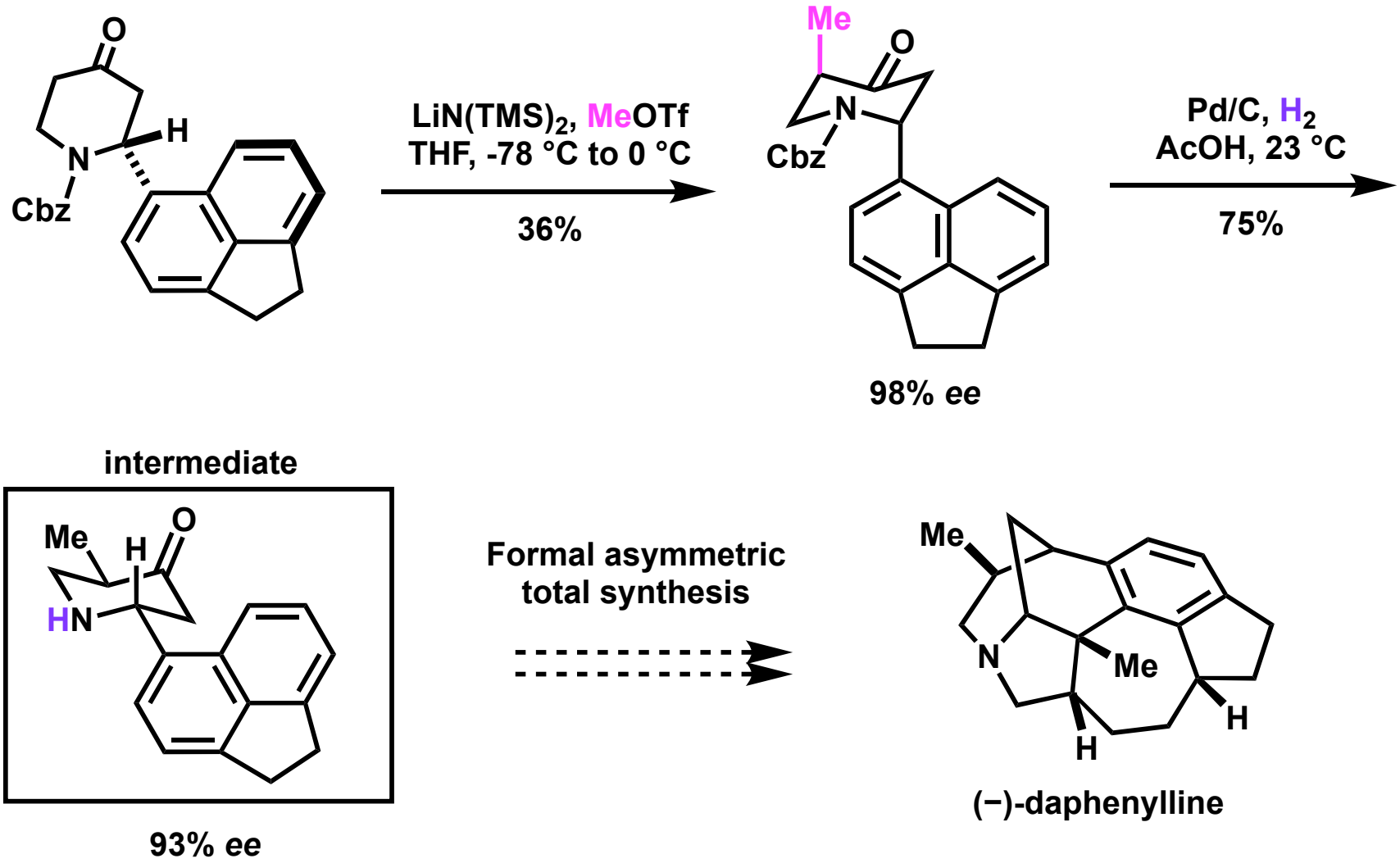
99% *ee*



(*S,S*)-Ph-BPE

1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.
2) Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240−6241.

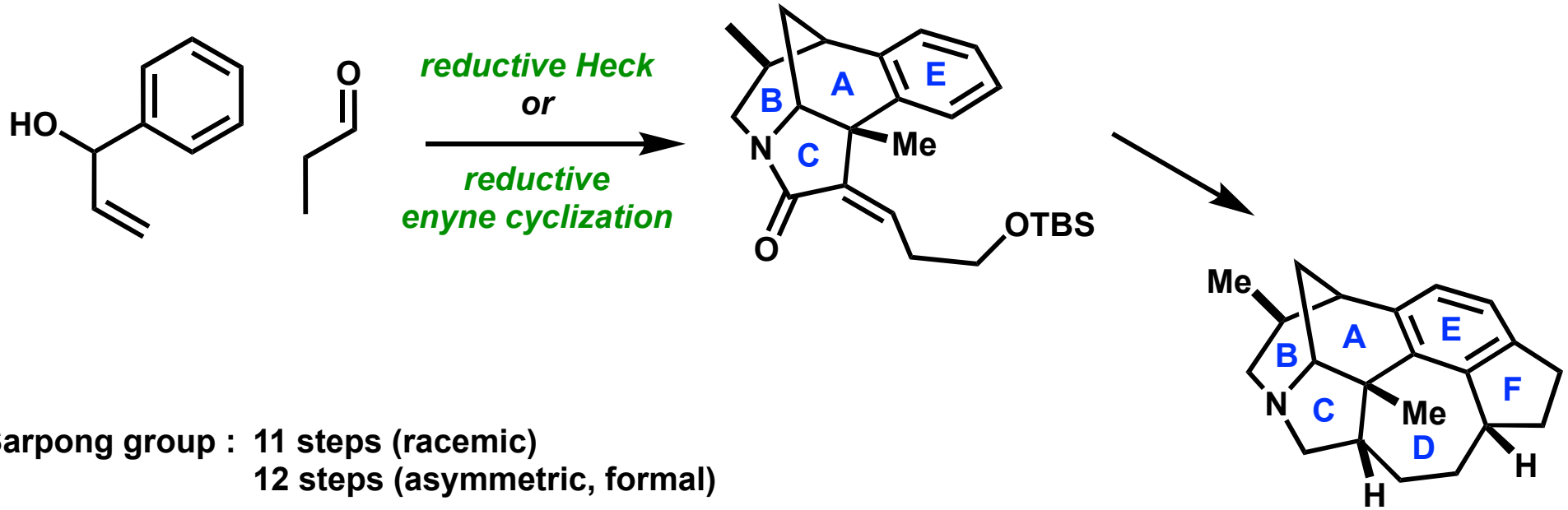
Synthesis of Enantioenriched intermediate



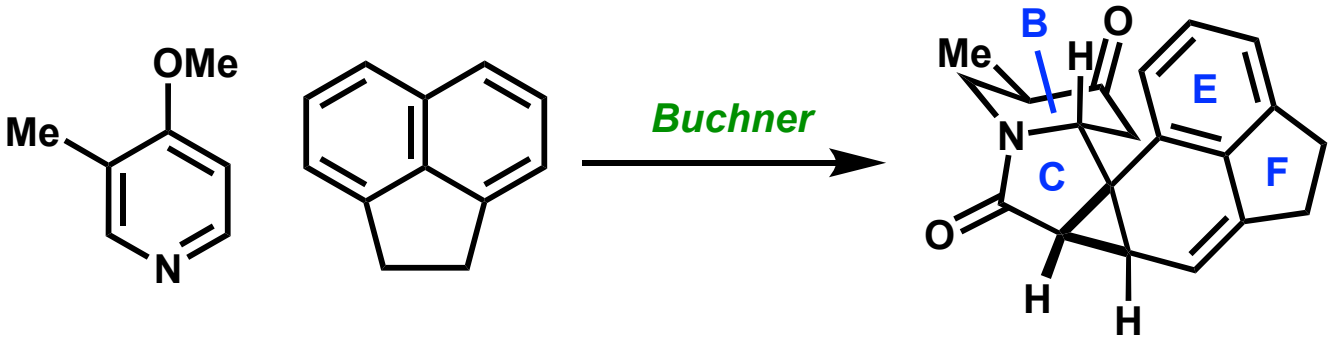
1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

Summary

Yang group : 14 steps (asymmetric)



Sarpong group : 11 steps (racemic)
12 steps (asymmetric, formal)



1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.

Appendix

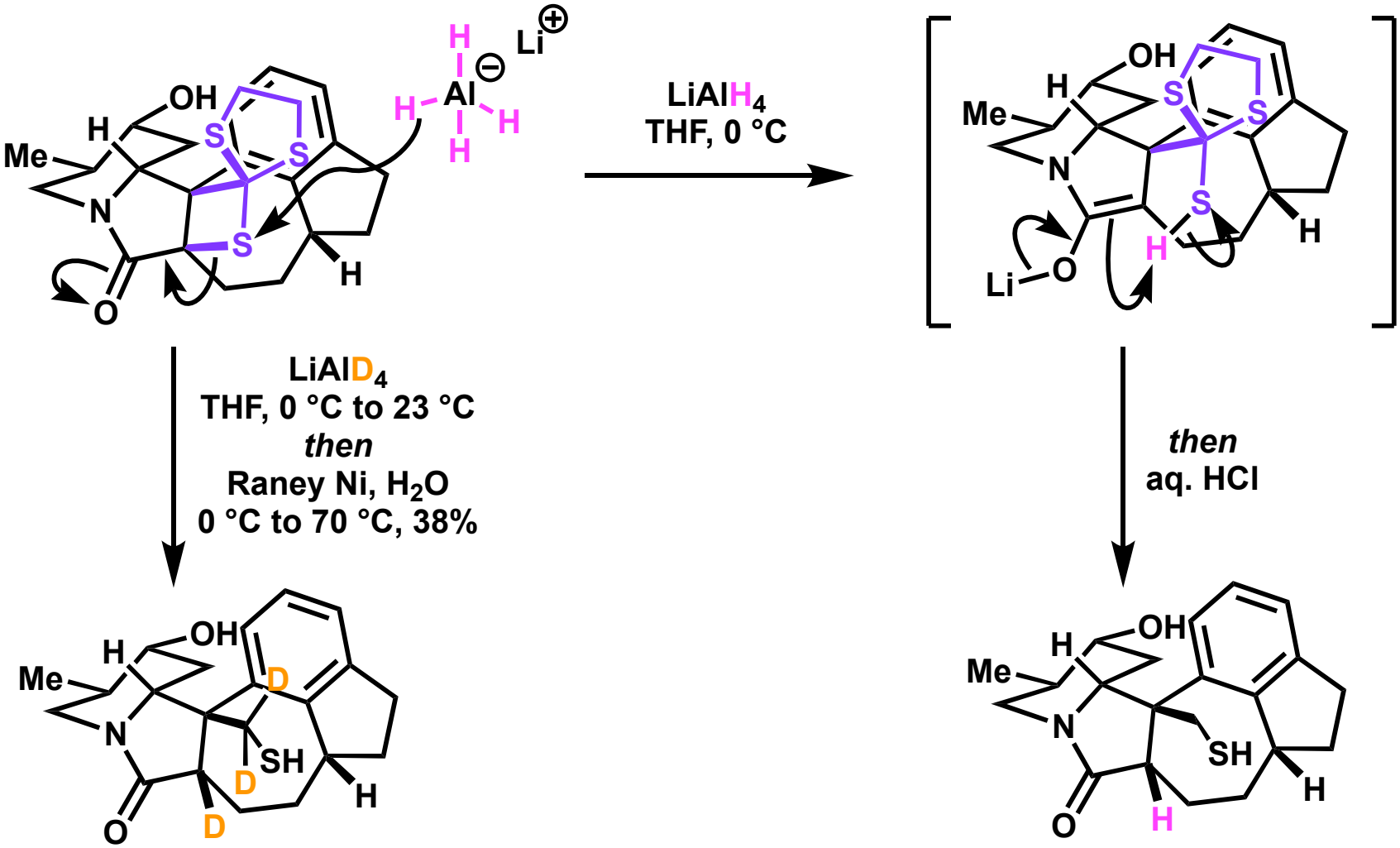
Optimization of Ir / amine Dual-catalyzed Allylation

entry	acid (mol%)	dr	ee	yield (%)
1	HCO_2H (75)	15:1	>99%	55
2	Cl_2CHCO_2H (75)	6:1	>99%	80
3	CH_3CO_2H (75)	-	-	trace
4	$ClCH_2CO_2H$ (75)	5.5:1	>99%	62
5	Cl_3CCO_2H (75)	2.5	>99%	25
6	F_2CHCO_2H (75)	4:1	>99%	60
7	$Cu(OTf)_2$ (10)	4.5:1	>99%	20
8	$Sc(OTf)_2$ (10)	15:1	>99%	16
9	$Zn(OTf)_2$ (10)	-	-	trace

(0.1 mmol scale)

1) Wu, B.; Yai, J.; Long, Z.; Tan, Z.; Liang, X.; Feng, L.; Wei, K.; Yang, Y. *J. Am. Chem. Soc.* **2024**, *146*, 1262-1268.
2) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. *Science* **2013**, *340*, 1065-1068.

Desulfurization



1) Wright, B. A.; Regni, A.; Chaisan, N.; Sarpong, R. *J. Am. Chem. Soc.* **2024**, *146*, 1813−1818.